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END OF SEARCH HISTORY

Dorlands Medical Dictionary on-line

Tween (Tween) (tw[emacr]n) trademark for preparations of polysorbates, used with a numerical suffix; e.g., *Tween 80* is a trademark for polysorbate 80.

polysorbate (poly·sor·bate) (pol″e-sor′b[amacr]t) a generic name for esters of sorbitol and its anhydrides condensed with polymers of ethylene oxide, used as surfactant agents: *p. 20,* $C_{58}H_{114}O_{26}$, is polyoxyethylene 20 sorbitan monolaurate; *p. 40,* $C_{62}H_{122}O_{26}$, is polyoxyethylene 20 sorbitan monopalmitate; *p. 60,* $C_{64}H_{126}O_{26}$, is polyethylene 20 sorbitan monostearate; *p. 65,* $C_{100}H_{194}O_{28}$, is polyethylene 20 sorbitan tristearate; *p. 80,* $C_{64}H_{124}O_{26}$, is polyethylene 20 sorbitan monooleate; *p. 85,* $C_{100}H_{188}O_{28}$, is polyethylene 20 sorbitan trioleate. *Polysorbates 20, 40, 60,* and *80* are official in NF.

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US005945098A

United States Patent [19]

Sarno et al.

[11] Patent Number: 5,945,098

[45] Date of Patent: *Aug. 31, 1999

[54] **STABLE INTRAVENOUSLY-ADMINISTRABLE IMMUNE GLOBULIN PREPARATION**

[75] Inventors: **Maria Erlinda C. Sarno**, Cerritos; **Rodolfo Anthony Vasquez**, Norwalk; **Sau-Gee Yung**, Rialto; **Clifford R. Graf**, Lakeview Terrace, all of Calif.

[73] Assignee: **Baxter International Inc.**, Deerfield, Ill.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/935,294**

[22] Filed: **Sep. 22, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/504,854, Jul. 20, 1995, abandoned, which is a continuation of application No. 08/317,214, Oct. 3, 1994, abandoned, which is a continuation of application No. 08/178,432, Jan. 6, 1994, abandoned, which is a continuation of application No. 07/866,089, Apr. 6, 1992, abandoned, which is a continuation of application No. 07/473,554, Feb. 1, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 38/21**

[52] **U.S. Cl.** **424/85.5**; 514/2; 514/12; 514/21; 530/387.1; 530/389.1; 530/380; 530/390.5

[58] **Field of Search** 424/85.5; 514/2, 514/12, 21; 530/387.1, 389.1, 380, 390.5

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[57] **ABSTRACT**

Stable, intravenously-administrable immune globulin preparations are stabilized against aggregation and polymerization and rendered isotonic with amino acid(s) and non-ionic detergents, polysorbate and polyethylene glycol. The immunoglobulins are derived from human or animal sources, or from hybridomas. Optional, additional stabilizers include various physiologically-acceptable carbohydrates and salts. Polyvinylpyrrolidone can be used in addition to the amino acid(s). Apart from the immunoglobulin itself, the preparations are otherwise essentially protein free. The preparations are useful in immunotherapy and as diagnostic reagents.

15 Claims, No Drawings

US-PAT-NO: 5643587
DOCUMENT-IDENTIFIER: US 5643587 A

TITLE: Composition and method for under-eye skin lightening

DATE-ISSUED: July 1, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Scancarella; Neil D.	Wyckoff	NJ		
Duffy; John A.	West Milford	NJ		
Garrison; Mark S.	White Plains	NY		
Menon; Gopinathan K.	Wayne	NJ		

US-CL-CURRENT: 424/401; 424/195.16, 424/62

CLAIMS:

What is claimed is:

1. A composition for topical treatment of skin discolorations found below the eyes, comprising:

(a) about 0.5 to about 10.0% live yeast cell extract,

(b) about 0.5 to about 10.0% magnesium ascorbyl phosphate,

(c) about 0.1 to about 5.0% tocopherol acetate,

(d) about 0.01 to about 1.0% retinol palmitate, and

(e) a vehicle which maintains active ingredient levels.

2. The composition of claim 1, comprising:

(a) about 8.5% emollient oils,

(b) about 7.5% waxes,

(c) about 5.0% glycerin,

(d) about 3.52% live yeast cell extract,

(e) about 3.0% magnesium ascorbyl phosphate,

(f) about 1.0 tocopherol acetate,

(g) about 0.5% retinol palmitate,

(h) about 0.7% vitamins,

(i) about 2.5% emulsifiers, and

(j) about 0.35% thickeners.

3. The composition of claim 2, wherein said emollient oils are selected from the group consisting of dioctyl maleate, grape and sunflower seed oils, and squalane; said waxes are selected from the group consisting of soya sterols, glyceryl monostearate, cetyl alcohol and myristyl myristate; said vitamins is vitamin K; said emulsifiers are selected from the group consisting of PEG 40 stearate, PEG 24 cholsteryl ether and polysorbate 20; and said thickeners are selected from the group consisting of xantham gum, Carbopols 934 and 941 and further comprising ascorbyl palmitate.

4. The composition of claim 1, comprising:

(a) about 10.0% emollient oils,

(b) about 5.0% glycerin,

(c) about 4.75% waxes,

(d) about 3.5% magnesium ascorbyl phosphate,

(e) about 3.25% live yeast cell extract,

(f) about 1.0 tocopherol acetate,

(g) about 0.25% retinol palmitate,

(h) about 0.8% vitamins,

(i) about 1.75% emulsifiers, and

(j) about 0.35% thickeners.

5. The composition of claim 4, wherein said emollient oils are selected from the group consisting of dioctyl maleate, grape and sunflower seed oils, and squalane; said waxes are selected from the group consisting of soya sterols, glyceryl monostearate, cetyl alcohol and myristyl myristate; said vitamins is vitamin K; said emulsifiers are selected from the group consisting of PEG 40 stearate, PEG 24 cholsteryl ether and polysorbate 20; and said thickeners are selected from the group consisting of xantham gum, Carbopols 934 and 941 and further comprising ascorbyl palmitate.

6. The composition of claim 1, comprising:

(a) about 1.5% emollient oils,

(b) about 1.5% glycerin,

(c) about 5.0% live yeast cell extract,

(d) about 2.0% magnesium ascorbyl phosphate,

(e) about 0.1 tocopherol acetate,

(f) about 0.1% retinol palmitate,

(g) about 0.2% vitamins,

(h) about 1.5% emulsifier, and

(j) about 0.75% thickeners.

7. The composition of claim 6, wherein said emollient oils are selected from the group consisting of dioctyl maleate, grape and sunflower seed oils, and squalane; said vitamins is vitamin K; said emulsifiers are selected from the group consisting of PEG 40 stearate, PEG 24 cholsteryl ether and polysorbate 20; and said thickeners are selected from the group consisting of xantham gum, Carbopols 934 and 941 and further comprising ascorbyl palmitate.

8. A method for topical treatment of skin discolorations found below the eyes comprising the application of a composition comprised of:

(a) about 0.5 to about 10.0% live yeast cell extract,

(b) about 0.5 to about 10.0% magnesium ascorbyl phosphate,

(c) about 0.09 to about 0.6% retinol palmitate,

(d) about 0.1 to about 5.0% tocopherol acetate, and

(e) a vehicle which maintains active ingredient levels.

9. The method of claim 8, wherein said composition comprises:

(a) about 8.5% emollient oils,

(b) about 7.5% waxes,

(c) about 5.0% glycerin,

(d) about 3.52% live yeast cell extract,

(e) about 3.0% magnesium ascorbyl phosphate,

(f) about 1.0 tocopherol acetate,

(g) about 0.5% retinol palmitate,

(h) about 0.7% vitamins,

(i) about 2.5% emulsifiers, and

(j) about 0.35% thickeners.

10. The method of claim 9, wherein said emollient oils are selected from the

group consisting of dioctyl maleate, grape and sunflower seed oils, and squalane; said waxes are selected from the group consisting of soya sterols, glyceryl monostearate, cetyl alcohol and myristyl myristate; said vitamins is vitamin K; said emulsifiers are selected from the group consisting of PEG 40 stearate, PEG 24 cholsteryl ether and polysorbate 20; and said thickeners are selected from the group consisting of xantham gum, Carbopols 934 and 941 and further comprising ascorbyl palmitate.

11. The method of claim 8, wherein said composition comprises:

(a) about 10.0% emollient oils,

(b) about 5.0% glycerin,

(c) about 4.75% waxes,

(d) about 3.5% magnesium ascorbyl phosphate,

(e) about 3.25% live yeast cell extract,

(f) about 1.0 tocopherol acetate,

(g) about 0.25% retinol palmitate,

(h) about 0.8% vitamins,

(i) about 1.75% emulsifiers, and

(j) about 0.35% thickeners.

12. The method of claim 11, wherein said emollient oils are selected from the group consisting of dioctyl maleate, grape and sunflower seed oils, and squalane; said waxes are selected from the group consisting of soya sterols, glyceryl monostearate, cetyl alcohol and myristyl myristate; said vitamins is vitamin K; said emulsifiers are selected from the group consisting of PEG 40 stearate, PEG 24 cholsteryl ether and polysorbate 20; and said thickeners are selected from the group consisting of xantham gum, Carbopols 934 and 941 and further comprising ascorbyl palmitate.

13. The method of claim 8, wherein said composition comprises:

(a) about 1.5% emollient oils,

(b) about 1.5% glycerin,

(c) about 5.0% live yeast cell extract,

(d) about 2.0% magnesium ascorbyl phosphate,

(e) about 0.1 tocopherol acetate,

(f) about 0.1% retinol palmitate,

(g) about 0.2% vitamins and vitamin derivatives,

(h) about 1.5% emulsifier, and

(j) about 0.75% thickeners.

14. The method of claim 13, wherein said emollient oils are selected from the group consisting of dioctyl maleate, grape and sunflower seed oils, and squalane; said vitamins is vitamin K; said emulsifiers are selected from the group consisting of PEG 40 stearate, PEG 24 cholsteryl ether and polysorbate 20; and said thickeners are selected from the group consisting of xantham gum, Carbopols 934 and 941 and further comprising ascorbyl palmitate.

15. A composition for topical treatment of skin discolorations found below the eyes, comprising:

(a) about 0.5 to about 10.0% live yeast cell extract,

(b) about 0.5 to about 10.0% magnesium ascorbyl phosphate, and

(c) a vehicle which maintains active ingredient levels.

16. The composition of claim 15, further comprising about 0.1 to about 5.0% tocopherol acetate.

17. The composition of claim 15, further comprising about 0.01 to about 1.0% retinol palmitate.

18. A method for topical treatment

First Hit

L8: Entry 141 of 160 File: DWPI Aug 31, 1999

DERWENT-ACC-NO: 1999-539002
DERWENT-WEEK: 199945

TITLE: A storage stable, intravenous-administrable immunoglobulin composition, useful in immunotherapy and in diagnostic processes

Basic Abstract Text (2):
DETAILED DESCRIPTION - A storage stable, intravenously-administrable immune globulin composition (I) comprises an aqueous solution of immune globulin, 0.1-0.3 M glycine, 0.0005-0.01% (w/v) polysorbate, and less than 0.2 g polyethylene glycol (PEG). (I) is essentially protein-free apart from the immune globulin.

First Hit

L8: Entry 158 of 160 File: DWPI Oct 29, 1986

DERWENT-ACC-NO: 1986-286406
DERWENT-WEEK: 199718

TITLE: Recovering pure protein from cultures of genetically modified yeast - by lysis in presence of nonionic detergent then pptn. of contaminants with polyethylene glycol

INVENTOR: GILLES, D; SIMONET, G ; VANWIJNEN, F

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PRIORITY-DATA: 1987US-0042914 (April 27, 1987), 1985US-0719601 (April 3, 1985)

Search Selected | Search ALL | Clear

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 199698 A	October 29, 1986	F	015	
PT 82219 A	September 16, 1986		000	
AU 8653786 A	October 9, 1986		000	
NO 8601234 A	October 27, 1986		000	
JP 61249398 A	November 6, 1986		000	
FI 8601251 A	October 4, 1986		000	
DK 8601522 A	October 4, 1986		000	
HU 40810 T	February 27, 1987		000	
ZA 8602374 A	May 18, 1987		000	
CN 8601798 A	October 15, 1986		000	
US 4683294 A	July 28, 1987		000	
ES 8706166 A	August 16, 1987		000	
DD 247685 A	July 15, 1987		000	
CS 8602233 A	February 15, 1988		000	
RO 95349 A	September 15, 1988		000	
US 4857317 A	August 15, 1989		000	
CA 1272457 A	August 7, 1990		000	
IL 78824 A	April 15, 1991		000	
SU 1604144 A	October 30, 1990		000	
EP 199698 B	August 28, 1991		000	
DE 3681058 G	October 2, 1991		000	

☐	JP 2512430 B2	July 3, 1996	008	C12P021/00
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DESIGNATED-STATES: AT BE CH DE FR GB IT LI LU NL SE AT BE CH DE FR GB IT LI LU NL SE

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EP 199698A	April 2, 1986	1986EP-0870041	
JP 61249398A	April 2, 1986	1986JP-0097518	
ZA 8602374A	April 1, 1986	1986ZA-0002374	
US 4683294A	April 3, 1985	1985US-0719601	
ES 8706166A	April 2, 1986	1986ES-0553633	
US 4857317A	April 27, 1987	1987US-0042914	
SU 1604144A	April 2, 1986	1986SU-4027296	
JP 2512430B2	April 2, 1986	1986JP-0077518	
JP 2512430B2		JP 61249398	Previous Publ.
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ABSTRACTED-PUB-NO: EP 199698A
BASIC-ABSTRACT:

A protein (I) bound to cells is extd. and purified from the supernatant of a genetically-modified yeast cell culture which has been lysed in presence of a nonionic detergent, comprises first adjusting the supernatant to pH 5.9-6.1. Then liq. or solid polyethylene glycol (PEG) is added until the supernatant becomes clear, then this treated with (1) a bivalent metal cation or (2), opt. after ultrafiltration, with (NH4)2SO4 to separate (I). Pref. liq. PEG is added to final concn. 10-35 vol.% or solid PEG to 6-12wt.%.

Pref. the clarified supernatant is treated with Ca or Mn ions to a final concn. of 80 mm. The ppte. is removed and the supernatant purified by ultrafiltration, qel permeation of the retentate and ion-exchange chromatography of the (I)-contg. peak. Opt. (I) is further purified by a second gel permeation step and centrifuging in a CsCe gradient. Alternatively, the clarified supernatant is mixed with (NH4)2SO4 to 40-50% satn. and (I) recovered in the PEG phase. This phase can be ultrafiltered and then subjected to gel permeation and ion-exchange chromatography. The nonionic detergent is esp. polysorbate 20.

USE/ADVANTAGE - The method is esp. applied to hepatitis B surface antigen (recovered in the form of micelles with a polysorbate, useful for making vaccines) or alpha-1-antitrypsin. Treatment with PEG provides efficient pptn. of most of the contaminants (typically 75% of proteins; 90% of polysaccharides, 94% of nucleic acids and 45% of lipids), while (I) remains in soln. A relatively high yield of pure (I) is achieved.

ABSTRACTED-PUB-NO: EP 199698B
EQUIVALENT-ABSTRACTS:

A process for the extraction and purification of a protein, bound to the cell, from the supernatant of a culture of genetically manipulated yeast cells which have produced said protein and burst in the presence of a non-ionic detergent, characterised in that the pH of the supernatant is adjusted to 6 (+/-0.1), liquid or solid polyethylene glycol is added until said supernatant has been clarified, and the clarified supernatant is treated either with a divalent metal cation, or after ultrafiltration if appropriate, with ammonium sulphate in order to separate out said protein. (19pp)

US 4683294A

Improved extn. and purificn. of cell-bound protein obtd. from the supernatant of engineered yeast cells producing such protein, comprises disruption using a nonionic detergent.

Process comprises (a) adjusting the supernatant to pH 6(+/-0.1); (b) adding liq. or solid polyethylene glycol up to the clarification of the supernatant; and (c) treating clarified prod. with a bivalent metal cation or with ammonium sulphate for sepg. the protein before or after ultrafiltration.

Pref. final concn. of liq. polyethylene glycol is 10-35% (v/v) and corresp. solid is 6-12% (w/v).

USE - For extn. and purificn. of hepatitis B surface antigen or alpha-1-antitrypsin. (7pp)d

US 4857317A

Hepatitis B surface antigen/polysorbate composite micelle contains 15-35% (w/w) polysorbate, as active ingredient in corresp. vaccine. Prodn. comprises (a) prepg. a supernatant of engineered yeast cells disrupted using a non-ionic detergent; (b) pptg. cqntominants by polyethylene glycol; and (c) treating supernatant obtd. with a bivalent metal cation, or with (NH4)2SO4 after eventual ultrafiltration. Hepatitis B virus surface antigen and alpha-1-antitrypsin are each thus extracted and purified.

USE - To protecting human against hepatitis B virus infection by administering intramuscularly. (7pp)

CHOSEN-DRAWING: Dwg.0/0

DERWENT-CLASS: A96 B04 D16
CPI-CODES: A05-H02; A12-W11L; B02-V02; B04-B04A5; B04-B04C1; D05-H07;

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(54) Procédé d'extraction et de purification de protéines issues de milieux de culture les produisant.

(57) Le procédé s'applique au surnageant de cellules de levure produites génétiquement et éclatées en présence d'un détergent non ionique; il comprend la précipitation des contaminants par le polyéthylène glycol et le traitement de ce surnageant par un cation métallique bivalent ou, après ultrafiltration éventuelle, par le sulfate d'ammonium.

EP 0 199 698 A2

Procédé d'extraction et de purification de protéines issues de milieux de culture les produisant

Domaine de l'invention

La présente invention a pour objet un procédé perfectionné d'extraction et de purification de protéines issues de milieux de culture les produisant; plus particulièrement, le procédé concerne l'extraction et la purification de l'antigène de surface du virus de l'hépatite B et de l'alpha-l-antitrypsine produits par des techniques d'ADN recombinant dans des cultures cellulaires produites génétiquement, plus particulièrement des cultures de souches de levure produites génétiquement.

Fondement de l'invention

Divers microorganismes, parmi lesquels les bactéries et les levures, peuvent être utilisés comme organismes hôtes pour différents plasmides contenant une molécule d'ADN renfermant une séquence nucléotidique codant pour une protéine spécifique. Parmi ces microorganismes, les levures sont actuellement préférées et d'un emploi courant. Par exemple, la demande de brevet européen publiée sous le numéro 0 106 828 décrit l'utilisation des souches de Saccharomyces cerevisiae pour la production de l'antigène de surface du virus de l'hépatite B (HBsAg) et la demande de brevet européen publiée sous le numéro 0 103 409 est relative à la production de l'alpha-l-antitrypsine au départ de plasmides de levure.

La production de protéines dans des souches de levure présente, en effet, de nets avantages par rapport à la production dans des souches bactériennes. Ces avantages proviennent de la croissance plus aisée des levures dans des fermenteurs à grande échelle et du fait que, contrairement aux bactéries, les levures ressemblent assez bien aux cellules de mammifères pour leur capacité d'additionner des groupes glucidiques aux protéines qui viennent d'être synthétisées.

Toutefois, l'extraction et la purification de la protéine issue d'une culture de levure donnent lieu à des problèmes techniques dus à la composition chimique plutôt complexe de la cellule de levure et plus particulièrement à cause de la présence des taux lipidiques élevés lorsqu'on prolonge la croissance de la levure pour améliorer le rendement de la production en polypeptides.

Par exemple, la paroi de Saccharomyces est supposée se composer de 3 couches : a) une couche interne de β-glucane insoluble en milieu alcalin, (b) une couche centrale de β-glucane alcalino-soluble et (c) une couche externe de glycoprotéine dans laquelle le glucide se compose de mannane phosphorylé; en dessous de la paroi se trouve une membrane cytoplasmique qui se compose d'un mélange très complexe constitué de lipides neutres (mono-, di-et triglycérides), de stérols libres et estérifiés, d'un sphingolipide complexe, de glycérophosphatides et de glycolipides neutres et acides; le noyau renferme de l'ADN, diverses espèces d'ARN et un polyphosphate; les vacuoles peuvent contenir une grande variété de composés de poids moléculaires élevés ou faibles; elles servent de vésicules de réserve destinées à de nombreuses hydrolases; les mitochondries sont riches en composés lipidiques, phospholipidiques et ergostéroliques en provenance du système membraneux et le cytoplasme contient entre autres de grandes quantités de ribosomes, de polyphosphates, de glycogènes et de nombreux enzymes de la glycolyse. La plupart des cellules de levure - (telle que l'espèce Saccharomyces) contiennent également une certaine quantité de lipide sous la forme de globules dont la quantité augmente dans les cultures prolongées.

De nombreux procédés à étapes multiples ont été décrits pour l'extraction et la purification de protéines issues de différentes sources. Des exemples de production de protéines par des microorganismes obtenus génétiquement sont ceux publiés par Th. STAEHELIN et al. (J. Biol. Chem. 256:9750-54; 1981), K. MURRAY et al. (The Embo J. 3:645-650; 1984) et R.A. HITZEMAN et al. (Nucl. Ac. Res. 11 :2745-2763; 1983).

En fait, lorsque la protéine produite est liée à la cellule, ces différents procédés impliquent 3 séries d'étapes.

Dans la première série d'étapes, la protéine désirée est isolée de l'intérieur de la cellule. A cette fin, les cellules sont soit lysées (p.ex. par traitement enzymatique) ou éclatées (p.ex. par des forces mécaniques telles que les forces de cisaillement (p.ex. la cellule de pression X ou la cellule de pression de French) ou agitées avec des billes de verre, avec addition éventuelle d'un détergent (voir par exemple K. MURRAY et al., loc. cit. et R.A. HITZEMAN et al., loc. cit.).

Dans la deuxième série d'étapes, le milieu est enrichi en protéine désirée, p.ex. par précipitation fractionnée par ajout de sulfate d'ammonium et/ou en présence de polyéthylène glycol.

Enfin, dans la troisième série d'étapes, tous les contaminants sont effectivement éliminés du milieu, p.ex. par une ou plusieurs opérations du genre ultrafiltration, chromatographie par échange d'ions et par filtration sur gel et centrifugation en gradient isopycnique.

Dans un tel procédé, il est évident que les contaminants accompagnant les protéines (cités par R.A. HITZEMAN et al., loc. cit.), les acides nucléiques et les lipides et plus particulièrement les taux de lipides élevés exercent une forte influence sur au moins une des étapes de la troisième série (p.e. l'ultrafiltration et la chromatographie sur colonne) et que les hydrolases doivent être rapidement éliminées du milieu. De plus, il a également été observé que la précipitation au sulfate d'ammonium n'est pas possible sans une délipidation préalable, étant donné que les lipides interfèrent dans cette précipitation.

En conséquence, il est de la première importance de pouvoir disposer d'une méthode par laquelle on puisse éliminer la plupart des contaminants dès le début de la troisième série d'étapes.

Parmi les procédés déjà décrits, certains citent l'utilisation du polyéthylène glycol comme agent de précipitation sélectif des protéines et un procédé de précipitation des lipoprotéines à partir du plasma en faisant appel aux interactions lipoprotéine-polyanionmétal a également été signalé.

La méthode de précipitation fractionnée des protéines à l'aide de polymères non ioniques hydrosolubles, en particulier le polyéthylène glycol - (PEG) a été introduite par POLSON et al. - (Biochem. Biophys. Acta 82:463-475; 1964) et discutée par divers auteurs. Parmi eux, W. HONIG et al. (Analyt. Biochem. 72:502-512; 1976) mentionnent que "la spécificité de la précipitation, c'est-à-dire le rapport de la protéine désirée et de la protéine totale peut être amélioré en utilisant des fractions de PEG d'un poids moléculaire moyen inférieur au PEG 6000 généralement employé". Néanmoins, quoique "des concentrés de protéines plasmatiques individuelles puissent être obtenus en agissant sur le pH", les auteurs ajoutent cependant que "la purification de mélanges protéiniques plus complexes tels que le surnageant d'un homogénat de cellule est considérablement plus médiocre".

P.R. FOSTER et al. (Biochim. Biophys. Acta 317: 505-516; 1973) ont décrit une méthode de précipitation d'enzymes à partir d'extraits cellulaires de Saccharomyces cerevisiae au moyen du PEG. Des méthodes de concentration et de purification de virus et de bactériophages à l'aide de PEG ont été publiées par B.P. VAJDA (Folia Microb. 23 :88-96; 1978) et G.J. LANCZ (Arch. Virusforsch. 42:303-306; 1973). Dans le domaine de l'isolement de l'antigène de l'hépatite, la purification de l'antigène de surface de l'hépatite B - (HBsAg) par une méthode comprenant deux traitements successifs avec le PEG 6000 a été décrite par Ph. ADAMOWICZ et al. (p. 37-49 INSERM SYMPOSIUM N° 18, HEPATITIS B VACCINE, Publ. ELSEVIER, Amsterdam, Holland, 1981). Dans cette méthode de purification de l'HBsAg au départ de plasma, les complexes immuns et la plupart des lipoprotéines sont, dans une première étape, précipités du sérum par le PEG 6000 à une concentration de 5.5 % et, dans une seconde étape, l'HBsAg est précipité du surnageant isolé par addition de PEG à une concentration finale de 10 %.

En ce qui concerne la littérature sur les brevets,

-le brevet des Etats-Unis d'Amérique N° 3790552 décrit une méthode d'élimination de l'antigène associé à l'hépatite à partir d'une fraction protéinique et qui comprend une étape dans laquelle on utilise du PEG ayant un poids moléculaire de 200 à 6000 à raison d'une quantité de 12 à 30 % (p/v) pour précipiter ledit antigène.

-le brevet des Etats-Unis d'Amérique N° 3951937 décrit un procédé de purification de l'antigène de l'hépatite B (HBAg) impliquant une double précipitation de l'HBAg au moyen de PEG (4 -4,5 % en poids) ayant un poids moléculaire d'au moins 600.

-le brevet des Etats-Unis d'Amérique N° 3994870 décrit une méthode de purification de l'antigène de l'hépatite B (HBAg) dans laquelle l'HBAg est précipité par addition de 4 à 4,5 % en poids de PEG et est ensuite soumis à une chromatographie d'affinité à l'aide de concanavalline A comme adsorbant chromatographique.

-la demande de brevet européen publiée sous le numéro 0 112 506 décrit un procédé de production d'un vaccin préventif de l'infection à l'hépatite B à partir de plasma et qui comprend une précipitation au sulfate d'ammonium suivie d'adsorption sur du silicate colloïdal et de deux étapes de précipitations successives avec du PEG (ayant un poids moléculaire de 2000 à 10000) à raison de 3 à 7 % (p/v) de manière à précipiter le virus de l'hépatite B et les immuns complexes et à raison de 15 à 20 % (p/v) dans le surnageant de manière à précipiter l'HBsAg.

-Dans le domaine de l'isolement de l'alpha-1-antitrypsine, la demande de brevet japonais 59 128335 (résumé Derwent 84-217127) décrit la précipitation d'alpha-1-antitrypsine à partir d'une fraction plasmatique par addition d'une quantité de 15 à 20 % (p/v) de PEG.

Ainsi qu'il a été mentionné ci-dessus, une méthode de précipitation des lipoprotéines par application des interactions lipoprotéine-polyanion-métal a également été signalée précédemment - (par exemple : M. BURSTEIN et al. Adv. Lip. Res., 11:67-108:1973 et A. VAN DALEN et al., Biochim. Biophys. Acta 147:421-427; 1967). Cette méthode est réalisée par interaction entre les lipoprotéines, un cation métallique bivalent et un polysaccharide acide et, dans ces conditions opératoires, la quantité de précipité est fonction de la concentration en cation métallique bivalent dans le milieu.

Description de l'invention

Le produit de départ utilisé dans le procédé de la présente invention (désigné également ici sous le nom d'"extrait brut") est le surnageant des cellules de levure produites génétiquement qui ont donné naissance à une protéine liée à la cellule et qui sont éclatées en présence d'un détergent non ionique, ainsi qu'il est bien connu dans la technique.

Conformément à la présente invention, on réalise alors la précipitation fractionnée par PEG - (désignée ci-après sous le nom de première étape) et, ensuite, soit une précipitation fractionnée par un cation métallique polyvalent (plus particulièrement un métal bivalent tel que le calcium ou le manganèse) soit un traitement au sulfate d'ammonium, ledit traitement au sulfate d'ammonium étant éventuellement précédé d'une ultrafiltration du surnageant provenant de la première étape.

o La présente invention résulte de la découverte que, lorsqu'on utilise du PEG solide (p.ex. PEG 6000) à une concentration de 6 à 12 % (p/v) pour extraire l'HBsAg à partir de cellules de levure produites génétiquement et éclatées en présence d'un détergent non ionique, l'HBsAg ne précipite pas. De plus, par addition ultérieure de sulfate d'ammonium, il se crée un système biphasé qui se caractérise par le fait que l'HBsAg est présent dans la phase PEG tandis que la majeure partie des contaminants se trouve dans la phase aqueuse. Ce résultat est surprenant étant donné que ces conditions opératoires devraient provoquer la précipitation de l'HBsAg en vertu de ce que l'art antérieur nous apprend généralement au sujet d'autres milieux bruts. Le premier objectif de la présente invention est donc d'utiliser le PEG comme solvant pour isoler la protéine désirée produite par des cultures de cellules de levure tandis que la majeure partie des contaminants sont éliminés par précipitation dans le milieu.

En ce qui concerne le poids moléculaire, le PEG existe soit sous forme solide, soit sous forme liquide, la limite entre les deux formes se situant autour d'un poids moléculaire de 1500.

Dans la première étape du procédé suivant la présente invention (qui pourrait être considérée également comme une étape de clarification), des PEGs ayant des poids moléculaires différents peuvent évidemment être utilisés en ajustant adéquatement leur concentration en fonction de leurs poids moléculaires respectifs.

Par exemple, la concentration en PEG varie, de préférence, de 6 à 12 % (p/v) lorsqu'on utilise du PEG solide (p.e. le PEG 6000) et de 10 à 35 % - (v/v) -et de préférence de 20 à 30 % (v/v) lorsqu'on utilise du PEG liquide (p.e. le PEG 300 ou 400). Néanmoins, l'utilisation de PEG liquide est préférable pour des raisons techniques parmi lesquelles la facilité de la dernière ultrafiltration.

En conséquence, la présente invention décrit un procédé d'extraction et de purification de protéines, plus particulièrement de l'HBsAg ou de l'alpha-l-antitrypsine, au départ du surnageant de cellules de levure éclatées en présence d'un détergent non ionique (de préférence un détergent du type polysorbate), ledit surnageant étant désigné ici par "extrait brut", lequel procédé comprend une première étape dans laquelle on ajoute 6 à 12 % (p/v) de PEG solide ou de préférence 10 à 25 % (v/v) de PEG liquide à l'extrait brut amené à pH 6 (± 0,1), les limites des concentrations en PEG susmentionnées étant principalement déterminées par le moment où la clarification est atteinte puisqu'une addition supplémentaire de PEG ne produit que des effets défavorables, c.à.d. une viscosité plus élevée du milieu et le risque d'une coprécipitation inopportune d'HBsAg ou d'alpha-l-antitrypsine.

Dans le procédé de la présente invention, le PEG est considéré comme un solvant organique polymérisé favorisant e.a. la précipitation des (lipo)-protéines dont le point isoélectrique se situe près du pH 6 et la solubilisation des autres (lipo)-protéines, c.à.d. celles qui présentent un point isoélectrique nettement différent et celles qui sont fortement hydrophobes.

La demanderesse a remarqué que l'étape de clarification par le PEG précipite environ 75 % des protéines contaminantes, 90 % des polysaccharides, 94 % des acides nucléiques et 45 % des lipides, tandis que c'est le contenu total en HBsAg ou en alpha-l-antitrypsine qui est pratiquement récupéré dans le surnageant.

Ainsi qu'il a été indiqué ci-dessus, la présente invention comprend une combinaison d'étapes dont la première est une étape de clarification en vue d'obtenir une solution partiellement purifiée et éventuellement quelque peu opalescente de la protéine désirée.

Dans la deuxième étape du procédé de la présente invention, la solution obtenue et partiellement purifiée est traitée soit par un cation métallique polyvalent - plus particulièrement un cation métallique bivalent -comme une solution aqueuse de chlorure de calcium ou de manganèse à une concentration finale de 30 mM, soit par du sulfate d'ammonium, ce traitement au sulfate d'ammonium étant effectué soit après ultrafiltration de la solution opalescente par addition de sulfate d'ammonium solide jusqu'à 40 à 50 % de saturation, suivant la méthode classique dite de relargage pour précipiter la protéine désirée laquelle peut être reprise dans un tampon phosphate, soit par addition de sulfate d'ammonium au surnageant contenant le PEG jusqu'à 40 à 50 % de saturation pour former un système biphasé contenant la protéine désirée dans la phase PEG.

Chacune de ces variations dans la deuxième série d'étapes donne lieu à une solution limpide en protéine désirée effectivement purifiée en ce qui concerne son contenu en polysaccharides, acides nucléiques, lipides et protéines contaminantes.

La solution ainsi obtenue peut ensuite être traitée dans la troisième série d'étapes classiques telle que définie ci-dessus, p.ex. ultrafiltration éventuelle, filtration sur gel et chromatographie sur colonne et, dans un mode de réalisation préféré de la présente invention, cette troisième série d'étapes comprend successivement une ultrafiltration, une première filtration sur gel, une chromatographie sur colonne échangeuse d'anion faiblement alcalin dotée de groupes diéthylaminoéthyle (DEAE) et une seconde filtration sur gel ou centrifugation sur gradient de chlorure de césium de manière à obtenir une solution d'HBsAg ou d'alpha-l-antitrypsine hautement purifiée et appropriée à un usage médical.

Lorsqu'on teste le produit isolé après la seconde perméation sur gel par électrophorèse sur gel de polyacrylamide sur dodécyl sulfate de sodium (SDS PAGE), on constate qu'il est pur à plus de 98 % en ce qui concerne la bande 23 K qui caractérise l'HBsAg issu de la levure.

En conséquence le premier avantage du procédé de la présente invention réside dans le fait qu'il élimine effectivement tous les polysaccharides, les acides nucléiques, les lipides et les matières protéiniques et un autre avantage de la présente invention est que la protéine désirée peut finalement être séparée avec un rendement relativement élevé.

Lorsque le procédé de la présente invention est appliqué à l'extrait brut d'HBsAg en provenance des cellules de levure produites génétiquement, l'HBsAg obtenu est lié au détergent non ionique en formant avec celui-ci des micelles composites d'un diamètre d'environ 17 à 20 nm et la demanderesse a découvert que le rapport exprimant la quantité de détergent non ionique sur la quantité de protéines, de lipides totaux et de polysorbate dans la micelle composite de polysorbate varie de 15 à 35 % (p/v) lorsque les analyses sont effectuées par méthode colorimétrique pour les protéines (LOWRY), les lipides totaux (ZOLLNER) et le détergent non ionique - (HUDDLESTON et ALLRED).

Les micelles composites obtenues par le procédé de la présente invention à l'aide d'un détergent non ionique de type polysorbate constituent des composés nouveaux qui font également l'objet de la présente invention; ils sont immunogènes et peuvent être présentés dans une forme vaccinale comparable à l'HBsAg classique ainsi qu'il est bien connu dans la technique pour la préparation du vaccin à base du virus de l'hépatite B.

L'invention est illustrée par les exemples suivants qui ne limitent en rien la porté de l'invention.

Exemple 1

Un culot de cellules de levure (3850 g) provenant d'une souche produite génétiquement et exprimant l'HBsAg et qui se sont développées jusqu'à l'obtention de 30 g de cellules en poids sec par litre de culture sont mises en suspension dans 7,12 litres d'une solution de Na_2HPO_4 (7.098 g l).

Cette suspension est additionnée de 142,5 ml d'une solution de EDTA à 4 % (p/v), 38,5 ml de polysorbate 20 et 385 ml d'isopropanol contenant 2,7 g de fluorure de phénylméthylsulfonyle - (FPMS). Le pH est ajusté à 8,1 (± 0,1) avec NaOH (10 % p/v dans l'eau). La suspension est refroidie dans un bain de glace et brisée par 2 passages à travers un homogénéiseur à billes de verre refroidi. L'homogénat (extrait brut) est ensuite centrifugé pendant 20 minutes à 13000 g.

On ajoute lentement, sous agitation, 2,5 l de PEG 400 à 7,7 l d'extrait brut que l'on maintient en dessous de 15° C. Le pH est ensuite ajusté à 6 (± 0,1) par addition d'acide acétique (5M) et le milieu est entreposé pendant une heure à 4° C avant d'être centrifugé à 7400-11000 g pendant 45 minutes.

Le surnageant est amené à pH 7 (± 0,05) avec NaOH N et on y ajoute 300 ml de $CaCl_2$ (c.à.d. 30 ml par litre de surnageant). Le pH est réajusté à 7 - (± 0,05) avec NaOH N et entreposé à 4° C jusqu'au lendemain. La suspension est centrifugée à 3600 g pendant 45 minutes et le surnageant est ultrafiltré dans un appareil AMICON DC (appareil vendu par AMICON CORP., DANVERS, MA, USA) équipé d'une cartouche ayant un cut-off de 100000 daltons et, par ce moyen, il est d'abord concentré jusqu'à 1/4 (1500 ml) de son volume initial. La solution est ensuite lavée de façon continue avec 12,5 ml de trométamol 10mM ajusté à pH 8 (± 0,1) par addition d'acide chlorhydrique N (ce tampon est désigné ci-après par trométamol pH 8) et additionné de PMSF (1 mM), d'isopropanol (2,5 % v/v) et d'EDTA (2 mM) (concentrations finales). Le rétentat est ensuite concentré ultérieurement jusqu'à 350 ml).

La solution concentrée est versée sur une colonne (diamètre 10 cm x 100 cm) contenant 7 l de FRACTOGEL®TSK HW65(F) (un gel semi-rigide composé de polymères vinyliques hydrophiles pourvus de nombreux groupes hydroxyles à la surface de la matrice, présentant une dimension de particules de l'ordre de 32 à 63 µm, fabriqué et vendu par E. Merck, Darmstadt, RFA) équilibré dans un tampon trométamol HCl 10 mM pH 7 (± 0,01) additionné de 5 % (v/v) d'éthylène glycol.

Le pic contenant l'HBsAg est versé sur une colonne (diamètre 5 cm x 30 cm) de 300 ml de FRACTOGEL® TSK DEAE 650 (M) (un échangeur anionique faiblement basique dans lequel les groupes diéthylaminoéthyle sont liés aux groupes hydroxyle de la matrice du FRACTOGEL TSK HW65 par des liaisons éthérées, fabriqué et vendu par E. Merck, Darmstadt, RFA) équilibré dans du trométamol pH 8 à 4° C. La colonne est lavée avec du trométamol pH 8 contenant NaCl (0,05 M) et l'HBsAg est élué avec NaCl (0,15 M) dans du trométamol pH 8.

L'éluat est appliqué sur une colonne de FRACTOGEL TSK HW65 (F) équilibrée avec un tampon Na_2HPO_4/NaH_2PO_4 (10 mM) pH 6,8 additionné de NaCl (150 mM) pour donner une solution de micelles composites du type HBsAg/polysorbate.

Le taux de purification obtenu à chaque étape de la purification est indiqué au tableau I.

TABLEAU I

Fraction	Vol (l)	Total en HBsAg par RIE (mg)	Total en protéi-nes (g)	Total en polysac-charides (g)	Total en acides nucléi-ques (mg)	Total en lipides (g)
Extrait brut Surna-geant	7,7	1232	259	114	32500	104
PEG Surna-geant	8,02	1100	64	9,5	641	53,7
$CaCl_2$	8	1190	37	3,8	512	27,2
Rétentat	.350	1320	26,7	.744	37,6	3,596
Pic HBsAg TSK	1,06	736	.935	.014	16	.352
Eluat TSK-DEAE	.15	722	.428	.0084	2,6	.275
Pic HBsAg TSK	.45	1117	.244	.0094	2	.179

RI3 : Radio-immuno essai

Le tableau II suivant résumé sommairement la composition ces micelles composites de 3 lots différents ce vaccins obenus par le procédé ci-dessus avec ou polysorbate 20.

TABLEAU II

Lot	Protéines (µg/ml) (A)	Total en lipides (µg/ml) (B)	Polysorbate 20 (ug/ml) (C)	Rapport C A/B/C
I	20	20	8,5	18
II	20	16	8,4	19
III	20	14,5	15,6	31

Exemple 2

On ajoute lentement 882 ml de PEG 400 à 2.650 l d'extrait brut préparé comme il est décrit à l'exemple 1 et on ajuste le pH à 6 (± 0,1). Le milieu est maintenu à 4° C pendant une heure et centrifugé ensuite à 7400 g. Le surnageant est concentré à 1000 ml sur un appareil AMICON DC équipé d'une cartouche ayant un cut-off de 100000 daltons et lavé ensuite avec 3 volumes de trométamol (20 mM) pH 8. Sous agitation et à 4° C. on ajoute ensuite lentement 277 g de sulfate d'ammonium en poudre au rétentat . Après 1 heure à 4° C, le précipité est centrifugé pendant 15 min. à 1000 g. Le sumageant est écarté et le précipité est dissout dans 400 ml de trométamol (20 mM) pH 8 additionné de 1 mM de PMSF. La solution est ultrafiltrée sur un appareil AMICON DC équipé d'une cartouche ayant un cut-off de 10^6 daltons. Le rétentat (500 ml) est lavé avec 2 volumes de trométamol pH 8 et appliqué ensuite sur une colonne contenant 300 ml de FRACTOGEL TSK DEAE 650M équilibré avec du trométamol pH 8. Lorsque le passage de l'échantillon est achevé, la colonne est lavée avec NaCl 0,05 M dans du trométamol pH 8 et un gradient linéaire en NaCl (0,05 M -0,5 M) est ensuite appliqué sur la colonne. La fraction éluée avec le NaCl 0,15 M contient l'HBsAg; elle est concentrée à 50 ml dans un appareil AMICON DC équipé d'une cartouche ayant un cut-off de 10000 daltons et appliquée sur une colonne (diamètre 50 x 100 cm) de Sepharose 4B-Cl (un gel d'agarose fabriqué et vendu par Pharmacia Fine Chemicals, Uppsala, Suède) équilibrée avec du trométamol (20 mM) pH 8 additionné de 5 % d'éthylène glycol pour donner une solution de micelles composites de type HBsAg/polysorbate.

Le taux de purification obtenu à chaque étape est indiqué au tableau III.

TABLEAU III

Fraction	Vol (ml)	Total en HBsAg par RIE (mg)	Total en protéines (g)	Total en polysaccharides (g)	Total en acides nucléiques (mg)
Extrait brut	2650	188	114,721	36,9	9250
Surnageant PEG	2530	160	22,755	3,321	536
Rétentat 10^5	1000	150	7,468	.181	175
AMS-culot	400	80,8	1,248	.0248	160
Rétentat 10^6	1000	72,4	.529	.029	88
Eluat TSK-DEAE	560	44	.157	<0,073	3
Pic HBsAg Sépharose 4B-CL	200	23	.030	.0003	.05

RIE : Radio-immuno essai

Exemple 3

On clarifie 2 litres d'extrait brut d'HBsAg avec du PEG 400 comme il est décrit à l'exemple 1. On y ajoute 450 g de sulfate d'ammonium (SAM) en poudre sous agitation (la concentration finale correspond à une saturation à 45 % en SAM. Après solubilisation du SAM, la solution est conservée à 4° C pendant une période de 3 heures au terme de laquelle on obtient deux phases distinctes que l'on sépare dans une ampoule à décantation : une phase supérieure limpide (jaune) (phase PEG 400) et une phase inférieure limpide (phase aqueuse), chacune des phases représentant environ ± 50 % du volume original. La phase aqueuse est éliminée et la phase supérieure est ultrafiltrée sur un appareil AMICON DC, comme il est décrit pour le surnageant du $CaCl_2$ à l'exemple 1. Le processus de purification est ensuite poursuivi ultérieurement comme il est décrit à l'exemple 1 pour donner une solution de micelles composites de type HBsAg:polysorbate.

Le taux de purification obtenu à chaque étape est indiqué au tableau IV.

TABLEAU IV

Fraction	Vol (ml)	Total en HBsAg par RIE (mg)	Total en protéines (g)	Total en polysaccharides (g)	Total en acides nucléiques (mg)
Extrait brut	2000	99	55	22	5588
Surnageant PEG	2000	92	13,2	5,68	243
phase PEG	1000	98	2,8	1,536	98
Retentat	50	98	1,5	.14	6,66
Pic HBsAg TSK	123	52.	.288	.0077	2,84
Eluat TSK-DEAE	25	54	.0377	.0011	.44
Pic HBsAg TSK	60	35	.0207	.00154	.39

RIE : Radio-immuno essai

Exemple 4

On clarifie 2 litres d'extrait brut en HBsAg avec du PEG 400 comme il est décrit à l'exemple 1. On y ajoute 450 g de sulfate d'ammonium (SAM) en poudre sous agitation (la concentration finale correspond à une saturation à 45 % en SAM). Après solubilisation du SAM, la solution est conservée à 4° C pendant une période de 3 heures au terme de laquelle on obtient deux phases distinctes que l'on sépare dans une ampoule à décantation : une phase supérieure limpide (jaune) (phase PEG 400) et une phase inférieure limpide (phase aqueuse), chacune des phases représentant environ ± 50 % du volume original. La phase aqueuse est éliminée et une partie aliquote d'un litre de la phase PEG - (phase supérieure) est diluée deux fois avec du trométamol 10 mM à pH 8 et appliquée sur une colonne conte nant 300 ml de gel du type FRACTOGEL TSK-DEAE 650 (M) équilibrée avec du trométamol à pH 8, à raison d'un débit de 100 ml par heure. Le gel est lavé avec du trométamol à pH 8 contenant NaCl 0,05 M et l'HBsAg est ensuite élué avec un gradient en NaCl (NaCl 0,05 à 0,5 M dans le trométamol à pH 8). Un pic HBsAg est élué avec NaCl 0,15 M et après concentration dans un appareil AMICON DC équipé d'une cartouche ayant un cut-off de 10000 daltons, le rétentat est appliqué sur une colonne (diamètre 5 x 100 cm) de Sépharose 4B-Cl équilibrée avec du trométamol pH 8 contenant 5 % (v/v) d'éthylène glycol pour donner un pic de micelles composites de type HBsAg/polysorbate/

Le taux de purification obtenu à chaque étape est indiqué au tableau V.

TABLEAU V

Fraction	Vol (ml)	Total en HBsAg par RIE (mg)	Total en protéines (g)	Total en polysaccharides (g)	Total en acides nucléiques (mg)
Extrait brut	2100	200	60,600	19,000	4860
phase PEG	1200	210	3,100	1,436	80
Eluat TSK-DEAE	460	134	.750	.0048	05
Pic HBsAg/ Sépharose 4B-CL	150	110	.120	.0014	0.3

RIE : Radio-immuno essai

Exemple 5

On clarifie 500 ml d'extrait brut en HBsAg par addition lente d'une solution de 50 g de PEG 6000 dans 160 ml d'eau à 4° C, sous agitation. On ajuste le pH à 6,1 par addition d'acide acétique 5M. Après une heure de stockage à 4° C, l'extrait est centrifugé pendant 15 min. à 7000 g. On ajoute ensuite, sous agitation, 157 g de sulfate d'ammonium en poudre au surnageant (la concentration finale correspond à 50 % de sulfate d'ammonium saturé). Après solubilisation, la solution est conservée à 4° C pendant une période de 3 heures au terme de laquelle on obtient deux phases distinctes que l'on sépare dans une ampoule à décantation. La phase supérieure (phase PEG contenant l'HBsAg) est diluée deux fois avec du trométamol à pH 8 et appliquée ensuite sur une colonne contenant 300 ml de gel de TSK-DEAE 650 (M) équilibrée avec du trométamol) pH 8 à raison d'un débit de 100 ml par heure. Le gel est lavé avec du trométamol à pH 8 contenant NaCl 0,15 M, concentré dans un appareil AMICON DC équipé d'une cartouche ayant un cut-off de 10000 daltons et le rétentat est appliqué ensuite sur une colonne (diamètre 5 x 100 cm) de 2 litres de FRACTOGEL TSK-HW65(F) équilibré avec du trométamol à pH 8 contenant 10 % (v/v) d'éthylène glycol pour donner une solution de micelles composites de type HBsAg/polysorbate.

Le taux de purification à chaque étape est indiqué au tableau VI.

TABLEAU VII

Fraction	Vol (ml)	Total en AAT par ELISA (mg)	Total en protéines (g)	Total en polysaccharides (g)
Extrait brut	120	180	4,018	.538
Surnageant PEG	100	212	1,300	.290
Surnageant $CaCl_2$	100	194	.660	.110
Eluat TSK-DEAE	520	180	.210	.0052

AAT : alpha-1-antitrypsine

Exemple 7

La technique est telle que décrite à l'exemple 1, mais on remplace les 300 ml de $CaCl_2$ M qui y sont spécifiés par 300 ml de $MnCl_2$ M. Les caractéristiques du produit final sont analogues à celles du produit obtenu à la fin de l'exemple 1.

Exemple 8

La technique est telle que décrite à l'exemple 1, mais on remplace les 38,5 ml de polysorbate 20 qui y sont spécifiés par 20 ml de Triton X-100 (un produit fabriqué par Rohm et Haas; Darmstadt, RFA). Les caractéristiques du produit final sont analogues à celles du produit obtenu à la fin de l'exemple 1.

Exemple 9

La technique est telle que décrite à l'exemple 1, mais on remplace les 38,5 ml de polysorbate 20 qui y sont spécifiés par 38,5 ml de polysorbate 80. Les caractéristiques du produit final sont analogues à celles du produit obtenu à la fin de l'exemple 1.

Exemple 10

La solution du micelle composite de type HBsAg obtenu à la fin de l'exemple 1 est ajustée à un contenu protéinique de 10 µg par millilitre par addition de NaCl, de tampon phosphate (Na_2HPO_4/NaH_2PO_4) et d'ALHYDROGEL® (un gel d'hydroxyde d'aluminium fabriqué et vendu par SUPERHOS Export Co. Copenhague, Danemark) jusqu'à des concentrations finales respectives de 0,9 % (p/v), 20 mM et 0,15 % (p/v) en $Al(OH)_3$, le pH final étant de 6,9. La préparation est stérilisée et répartie dans des fioles en verre de 2 ml contenant chacune une dose unitaire d'un ml de vaccin.

Exemple 11

Les doses unitaires du vaccin de l'exemple 10 ont été administrées par voie intramusculaire à deux séries de sujets séronégatifs à raison de 2 injections successives, à un mois d'intervalle. Bien que ces injections devraient être considérées comme une administration de sensibilisation qui devrait être suivie d'un rappel, p.ex. 2 mois après la première injection, une réponse immunitaire positive a déjà été observée respectivement un et deux mois après la première administration.

Dans la première série (comprenant 32 sujets séronégatifs), un mois après la première administration, le tuax de séroconversion était de 20/32, c'est-à-dire de 62,5 % avec un titre géométrique moyen (TGM) de 9.95 unités milli-internationales (UMI) et un mois après la seconde administration, le taux de séroconversion était de 31/32, c'est-à-dire de 96,9 % avec un TGM de 36 UMI.

Dans la seconde série (comprenant 46 sujets séronégatifs), un mois après la première administration, le taux de séroconversion était de 31/46, c'est-à-dire de 67,4 % avec un TGM de 13,6 UMI.

L'enregistrement des signes et symptômes cliniques chez les vaccinés n'a révélé aucune élévation de température et aucune réaction à l'endroit de l'administration.

Revendications

Revendications pour les pays contractants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Procédé d'extraction et de purification d'une protéine liée à la cellule à partir du surnageant d'une culture de cellules de levure manipulées génétiquement ayant produit ladite protéine et éclatées en présence d'un détergent non ionique, caractérisé en ce qu'on ajuste le pH du surnageant à 6 (± 0,1), on y ajoute du polyéthylène glycol liquide ou solide jusqu'à clarification dudit surnageant et on traite le surnageant clarifié soit par un cation métallique bivalent, soit, après ultrafiltration éventuelle, par du sulfate d'ammonium pour séparer ladite protéine.

2. Procédé suivant la revendication 1, dans lequel on ajoute du polyéthylène glycol liquide à une concentration finale comprise entre 10 et 35 % (v/v).

3. Procédé suivant la revendication 2, dans lequel on ajoute du polyéthylène glycol solide à une concentration finale comprise entre 6 et 12 % (p/v).

4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel la protéine est l'antigène de surface de l'hépatite B.

5. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel la protéine est l'alpha-1-antitrypsine.

6. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel le surnageant clarifié est traité par un cation métallique bivalent.

7. Procédé suivant la revendication 6, dans lequel le cation métallique bivalent est le cation calcium ou manganèse.

8. Procédé suivant l'une quelconque des revendications 6 et 7, qui comprend en outre la séparation du précipité, l'ultrafiltration de la solution, la perméation sur gel du rétentat, la chromatographie sur échangeurs d'ions du pic contenant la protéine et éventuellement une seconde perméation sur gel ou une centrifugation sur gradient de chlorure de cesium.

9. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel on traite le surnageant clarifié par du sulfate d'ammonium jusqu'à 40 à 50 % de saturation et on isole la protéine purifiée dans la phase polyéthylène glycol.

10. Procédé suivant la revendication 9, dans lequel la phase polyéthylène glycol est soumise en outre à une éventuelle ultrafiltration suivie d'une perméation sur gel et d'une chromatographie sur échangeurs d'ions.

11. Procédé suivant la revendication 9, dans lequel la phase polyéthylène glycol est soumise en outre à une éventuelle ultrafiltration suivie d'une chromatographie sur échangeurs d'ions et d'une perméation sur gel.

12. Procédé suivant la revendication 2, dans lequel le surnageant clarifié est soumis à une ultrafiltration et le rétentat est traité par du sulfate d'ammonium jusqu'à 40 à 50 % de saturation afin de pré cipiter la protéine qui est reprise dans un tampon adéquat.

13. Procédé suivant la revendication 12 qui comprend en outre l'ultrafiltratration, la perméation sur gel et la chromatographie sur échangeurs d'ions.

14. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel le détergent non ionique est un polysorbate.

15. Procédé suivant la revendication 14, dans lequel le polysorbate est le polysorbate 20.

16. Micelle composite à base d'antigène de surface de l'hépatite B et de polysorbate contenant de 15 à 35 % (p/p) de polysorbate.

17. Vaccin contre l'hépatite B contenant à titre d'ingrédient actif une micelle composite suivant la revendication 16.

Revendications pour l'Etat Contractant AT

1. Procédé d'extraction et de purification d'une protéine liée à la cellule à partir du surnageant d'une culture de cellules de levure manipulées génétiquement ayant produit ladite protéine et éclatées en présence d'un détergent non ionique, caractérisé en ce qu'on ajuste le pH du surnageant à 6 (± 0,1), on y ajoute du polyéthylène glycol liquide ou solide jusqu'à clarification dudit surna-

geant et on traite le surnageant clarifié soit par un cation métallique bivalent, soit, après ultrafiltration éventuelle, par du sulfate d'ammonium pour séparer ladite protéine.

2. Procédé suivant la revendication 1, dans lequel on ajoute du polyéthylène glycol liquide à une concentration finale comprise entre 10 et 35 % - (v/v).

3. Procédé suivant la revendication 2, dans lequel on ajoute du polyéthylène glycol solide à une concentration finale comprise entre 6 et 12 % (p/v).

4. Procédé suivant l'une quelconque des revendications 1 à 3 , dans lequel la protéine est l'antigène de surface de l'hépatite B.

5. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel la protéine est l'alpha-l-antitrypsine.

6. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel le surnageant clarifié est traité par un cation métallique bivalent.

7. Procédé suivant la revendication 6, dans lequel le cation métallique bivalent est le cation calcium ou manganèse.

8. Procédé suivant l'une quelconque des revendications 6 et 7, qui comprend en outre la séparation du précipité, l'ultrafiltration de la solution, la perméation sur gel du rétentat, la chromatographie sur échangeurs d'ions du pic contenant la protéine et éventuellement une seconde perméation sur gel ou une centrifugation sur gradient de chlorure de cesium.

9. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel on traite le surnageant clarifié par du sulfate d'ammonium jusqu'à 40 à 50 % de saturation et on isole la protéine purifiée dans la phase polyéthylène glycol.

10. Procédé suivant la revendication 9, dans lequel la phase polyéthylène glycol est soumise en outre à une éventuelle ultrafiltration suivie d'une perméation sur gel et d'une chromatographie sur échangeurs d'ions.

11. Procédé suivant la revendication 9, dans lequel la phase polyéthylène glycol est soumise en outre à une éventuelle ultrafiltration suivie d'une chromatographie sur échangeurs d'ions et d'une perméation sur gel.

12. Procédé suivant la revendication 2, dans lequel le surnageant clarifié est soumis à une ultrafiltration et le rétentat est traité par du sulfate d'ammonium jusqu'à 40 à 50 % de saturation afin de pré cipiter la protéine qui est reprise dans un tampon adéquat.

13. Procédé suivant la revendication 12 qui comprend en outre l'ultrafiltratration, la perméation sur gel et la chromatographie sur échangeurs d'ions.

14. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel le détergent non ionique est un polysorbate.

15. Procédé suivant la revendication 14, dans lequel le polysorbate est le polysorbate 20.

DERWENT-ACC-NO: 1990-192954
DERWENT-WEEK: 199025

TITLE: Solid unit dosage form of piperidino-alkanol cpds. - contg. surfactant and carbonate salt for ready bio-availability of antihistamine, broncho dilator or anti-allergy agent

INVENTOR: DOMET, J; SHAH, D N

PRIORITY-DATA: 1989US-0325254 (March 17, 1989), 1987US-0105928 (October 7, 1987), 1987US-0117166 (November 4, 1987), 1988US-0152689 (February 5, 1988)

PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	US 4929605 A	May 29, 1990		000	

INT-CL (IPC): A61K 9/20; A61K 31/44; A61K 47/00

ABSTRACTED-PUB-NO: DE 3873011G
BASIC-ABSTRACT:

A pharmaceutical compsn. in solid unit dosage form comprises (a) a therapeutically effective amt. of a piperidino alkanol cpd. or one of its salts, (b) a non-ionic or cationic surfactant in an amt. of 0.1-6 wt.% of the compsn., and (c) a carbonate salt in an amt. of 2-50 wt.% of the compsn.

Pref. cpds. (a) include alpha-(4-(1,1-dimethylethyl)phenyl) -4-hydroxydiphenylmethyl -1-piperidine butanol, which may be present, e.g. in an amt. of 10-120mg, esp. 60 or 120 mg. The pref. carbonate is calcium carbonate, used in amt. of 2-25 wt.%, more pref. 12-18 wt.% and esp. 15 wt.%. Non-ionic surfactant is pref. present in an amt. of 2-4 wt.%, esp. 3 wt.% and the pref. surfactant is polysorbate 80. There may also be present microcrystalline cellulose (35 wt.%), pregelatinised corn starch (30 wt.%), sodium starch glycolate (5 wt.%) and magnesium stearate (0.5 wt.%). A suitable cationic surfactant is cetyl pyridinium chloride.

USE/ADVANTAGE - Cpds. (a) are antihistamines, antiallergy agents and bronchodilators. The present compsns. contg. them allow efficient and immediate absorption and bioavailability of the cpds. after their oral admin.
ABSTRACTED-PUB-NO:

EP 310999B EQUIVALENT-ABSTRACTS:

Pharmaceutical compsn. in solid unit dosage form comprises (1) at least one piperidino-alkanol cpd. (I), or its pharmaceutically acceptable salt; (2) at least one surfactant at 0.1-6 wt.% and (3) 2-50 wt.% CaCO3. Specifically, (I) is alpha-(4-(1,1-dimethylethyl) phenyl-4-(hydroxydiphen- yl methyl)- 1-piperidino-butanol (Ia); the surfactant is nonionic or cationic (pref. 'Polysorbate 80', polyethylene glycol (PEG) or cetylpyridinium chloride) at 0.5-4, esp. 1-3 wt.% and CaCO3 is 2-25, esp. 12-15, wt.%.
USE/ADVANTAGE - (I) are variously useful as antihistamines, antiallergic agents or bronchodilators, particularly (Ia) is used to treat seasonal allergic rhinitis. Although (I) have very low solubility in water, in these compsns. they provide efficient and immediate absorption and bioavailability, following oral

admin. Pref. unit doses contain about 60 or 120 mg (I).

A pharmaceutical composition in solid unit dosage form comprising a) a therapeutically effective amount of at least one piperidinoalkanol compound of the formula (1), wherein R1 is hydrogen or hydroxy; R2 is hydrogen; or R1 and R2 taken together form a second bond between the carbon atoms bearing R1 and R2; n is an integer of from 1 to 5; in case n is an integer of from 1 to 3, Z is thienyl, phenyl or substituted phenyl wherein the substituents on the substituted phenyl may be attached at the ortho, meta, or para positions of the substituted phenyl ring and are selected from a halogen atom, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, a di(lower alkyl)amino group, or a saturated monocyclic heterocyclic ring selected from pyrrolidino, piperidino, morpholino, or N-(lower alkyl)-piperizino; or in case n is an integer of from 1 to 5, Z is a gp. of formula (i), wherein R3 is -CH3, -CH2OH, -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched; each of A and B is hydrogen or hydroxy; with the provisos that at least one of A or B is hydrogen and one of A or B is other than hydrogen when R3 is -CH3; and pharmaceutically acceptable salts and individual optical isomers thereof, b) one or more nonionic surfactants in an amount of from 0.1% to 6% by weight of the composition, c) calcium carbonate in an amount of from 2% to 50% by weight of the composition.

US 4929605A

First Hit

L8: Entry 34 of 160 File: PGPB Dec 25, 2003

DOCUMENT-IDENTIFIER: US 20030235595 A1
TITLE: Oil-containing, orally administrable pharmaceutical composition for improved delivery of a therapeutic agent

CLAIMS:

22. The composition of claim 21, wherein the at least one hydrophilic surfactant is selected from polysorbate 80, PEG-35 castor oil, and PEG-40 castor oil.

76. A pharmaceutical composition comprising: (a) a carrier comprising glyceryl tricaprylate/caprate, at least one hydrophilic surfactant selected from the group consisting of tocopheryl PEG-1000 succinate, polysorbate 80, PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-8 caprylic/capric glycerides, lauroyl macrogol-32 glycerides, stearoyl macrogol glyceride, and mixtures thereof; and at least one hydrophobic surfactant selected from the group consisting of glyceryl caprylate, glyceryl caprylate/caprate and mixtures thereof; and (b) a therapeutically effective amount of fenofibrate, wherein the triglyceride and surfactants are present in amounts that are pharmaceutically acceptable and selected so that upon admixture of the composition with an aqueous solution in an aqueous solution to composition ratio of about 100:1 by weight, a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm is provided.

77. The composition of claim 76, wherein the at least one hydrophilic surfactant is selected from the group consisting of tocopheryl PEG-1000 succinate, polysorbate 80, and mixtures thereof.

First Hit

L8: Entry 34 of 160 File: PGPB Dec 25, 2003

PGPUB-DOCUMENT-NUMBER: 20030235595
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030235595 A1

TITLE: Oil-containing, orally administrable pharmaceutical composition for improved delivery of a therapeutic agent

PUBLICATION-DATE: December 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chen, Feng-Jing	Salt Lake City	UT	US	
Patel, Mahesh V.	Salt Lake City	UT	US	

APPL-NO: 10/ 397969 [PALM]
DATE FILED: March 25, 2003

RELATED-US-APPL-DATA:
Application 10/397969 is a continuation-in-part-of US application 09/877541, filed June 8, 2001, PENDING
Application 09/877541 is a continuation-in-part-of US application 09/345615, filed June 30, 1999, US Patent No. 6267985
Application 09/877541 is a continuation-in-part-of US application 09/751968, filed December 29, 2000, US Patent No. 6458383
Application 09/751968 is a continuation-in-part-of US application 09/375636, filed August 17, 1999, US Patent No. 6309663

INT-CL: [07] A61 K 9/00, A61 K 31/192

US-CL-PUBLISHED: 424/400; 514/571
US-CL-CURRENT: 424/400; 514/571

ABSTRACT:

The present invention relates to oral pharmaceutical compositions and methods for improved delivery of therapeutic agents, e.g., lipid-regulating agents. Compositions of the present invention include a carrier, where the carrier contains a combination of a triglyceride and at least two surfactants, at least one of which is hydrophilic. Upon dilution with an aqueous medium, the composition forms a clear, aqueous dispersion. The invention also pertains to methods for treating lipid disorders such as hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia by oral administration of the compositions provided.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/877,541, filed Jun. 8, 2001, which is a continuation-in-part of U.S. patent application Ser. No. 09/345,615, filed Jun. 30, 1999, issued on Jul. 31, 2001 as

-DOCUMENT-NUMBER: 20030138491
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030138491 A1

TITLE: Microencapsulation and sustained release of biologically active acid-stable or free sulfhydryl-containing proteins

PUBLICATION-DATE: July 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Tracy, Mark A.	Arlington	MA	US	
Ward, Kevin L.	Arlington	MA	US	
Scher, David S.	Hudson	MA	US	
Johnson, J. Keith	Hudson	MA	US	

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
Alkermes Controlled Therapeutics, Inc.	Cambridge	MA		02

APPL-NO: 10/ 217953 [PALM]
DATE FILED: August 13, 2002

RELATED-US-APPL-DATA:
Application 10/217953 is a continuation-of US application 09/501934, filed February 10, 2000, US Patent No. 6465425

INT-CL: [07] A61 K 38/21, A61 K 9/14

US-CL-PUBLISHED: 424/486; 424/85.6
US-CL-CURRENT: 424/486; 424/85.6

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

This invention relates to sustained release compositions, and methods of forming and using said compositions, for the sustained release of biologically active acid-stable or free sulfhydryl-containing proteins, in particular .beta.-IFN. The sustained release composition of this invention comprises a biocompatible polymer having dispersed therein a stabilized biologically active acid-stable or free sulfhydryl-containing protein formulation and a nonionic polymer surfactant.

The method of the invention, for forming a composition for the sustained release of biologically active acid-stable or free sulfhydryl-containing protein, in particular .beta.-IFN, includes dissolving a polymer in a polymer solvent to form a polymer solution, adding a stabilized biologically active acid-stable or free sulfhydryl-containing protein formulation and a nonionic surfactant to the polymer solution, and then solidifying the polymer to form a polymer matrix containing the stabilized biologically active acid-

stable or free sulfhydryl-containing protein formulation, and a nonionic surfactant.

The method of using the sustained release composition of the present invention comprises providing a therapeutically effective blood level of biologically active acid-stable or free sulfhydryl-containing protein in a subject for a sustained period by administering to the subject a dose of the sustained release composition described herein.

RELATED APPLICATION

[0001] This application is a continuation of U.S. application Ser. No. 09/501,934, filed Feb. 10, 2000. The entire teachings of the above application are incorporated herein by reference.

DOCUMENT-IDENTIFIER: US 20030138491 A1
TITLE: Microencapsulation and sustained release of biologically active acid-stable or free sulfhydryl-containing proteins

CLAIMS:

10. The sustained release composition of claim 1 wherein the surfactant is selected from the group consisting of: poloxamers, polysorbates, polyethyleneglycols, polyoxyethlene fatty acid esters, bile salts, benzalkonium chloride, polyoxyethylene (40) monostearate and combinations thereof.

21. The sustained release composition of claim 20 wherein the nonionic surfactant is selected from the group consisting of: poloxamers, polysorbates, polyethyleneglycol, polyoxyethlene fatty acid esters and combinations thereof.

DOCUMENT-IDENTIFIER: US 20030064030 A1
TITLE: Ultrasound contrast agents and methods of making and using them

CLAIMS:

75. A vesicular composition according to claim 74 wherein said polymer is selected from the group consisting of poly(ethylene glycol) (PEG), poly(vinylpyrrolidone), polyoxomers, polysorbate and polyvinyl alcohol.

PGPUB-DOCUMENT-NUMBER: 20030064030
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030064030 A1

TITLE: Ultrasound contrast agents and methods of making and using them

PUBLICATION-DATE: April 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schneider, Michel	Troinex		CH	
Yan, Feng	Carouge		CH	
Garcel, Nadine	Ambilly		FR	
Grenier, Pascal	Ambilly		FR	
Puginier, Jerome	Le Chable-Beaumont		FR	
Barrau, Marie-Bernadette	Geneve		CH	
Bussat, Philippe	Feigeres		FR	
hybl, Eva	Heidelberg		DE	
Bichon, Daniel	Montpellier		FR	

APPL-NO: 10/ 102684 [PALM]
DATE FILED: March 22, 2002

RELATED-US-APPL-DATA:
Application 10/102684 is a continuation-of US application 09/225293, filed January 5, 1999, ABANDONED
Application 09/225293 is a continuation-in-part-of US application 08/033435, filed March 18, 1993, ABANDONED
Application 08/033435 is a division-of US application 07/695343, filed May 3, 1991, ABANDONED
Application 10/102684 is a continuation-of US application 09/225293, filed January 5, 1999, ABANDONED
Application 09/225293 is a continuation-in-part-of US application 08/853936, filed May 9, 1997, US Patent No. 6110443
Application 08/853936 is a division-of US application 08/456385, filed June 1, 1995, US Patent No. 5658551
Application 08/456385 is a division-of US application 08/315347, filed September 30, 1994, US Patent No. 5531980
Application 08/315347 is a division-of US application 08/128540, filed September 29, 1993, US Patent No. 5380519
Application 08/128540 is a division-of US application 07/775989, filed November 20, 1991, US Patent No. 5271928
Application 10/102684 is a continuation-of US application 09/225293, filed January 5, 1999, ABANDONED
Application 09/225293 is a continuation-in-part-of US application 08/740653, filed October 31, 1996, PENDING
Application 08/740653 is a division-of US application 08/350588, filed December 6, 1994, US Patent No. 5518991
Application 08/350588 is a division-of US application 07/991237, filed December 16, 1992, US Patent

No. 5413774

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
EP	90810262.7	1990EP-90810262.7	April 2, 1990
EP	90810367.4	1990EP-90810367.4	May 18, 1990
WO	PCT/EP91/00620	1991WO-PCT/EP91/00620	April 2, 1991
EP	92810046.0	1992EP-92810046.0	January 23, 1992

INT-CL: [07] A61 L 9/04

US-CL-PUBLISHED: 424/45
US-CL-CURRENT: 424/45

ABSTRACT:

Gas or air filled microbubble suspensions in aqueous phases usable as imaging contrast agents in ultrasonic echography. They contain laminarized surfactants and, optionally, hydrophilic stabilizers. The laminarized surfactants can be in the form of liposomes. The suspensions are obtained by exposing the laminarized surfactants to air or a gas before or after admixing with an aqueous phase. One can impart outstanding resistance against collapse under pressure to these gas-filled microbubbles used as contrast agents in ultrasonic echography by using as fillers gases whose solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight does not exceed 0.003.

[0001] This application is a continuation-in-part of Ser. No. 08/033,435, filed Mar. 18, 1993, which is a divisional of Ser. No. 07/695,343, filed May 3, 1991, which originated from EP 90810367.4, filed May 18, 1990. This application is also a continuation-in-part of Ser. No. 08/853,936, filed May 9, 1997, which is still pending, which is a divisional of Ser. No. 08/456,385, filed Jun. 1, 1995, now U.S. Pat. No. 5,658,551, which is a divisional of Ser. No. 08/315,347, filed Sep. 30, 1994, now U.S. Pat. No. 5,531,980, which is a divisional of Ser. No. 08/128,540, filed Sep. 29, 1993, now U.S. Pat. No. 5,380,519, which is a divisional of Ser. No. 07/775,989, filed Nov. 20, 1991, now U.S. Pat. No. 5,271,928, which originated from PCT/EP91/00620, filed Apr. 2, 1991, and EP 90810262.7, filed Apr. 2, 1990. This application is also a continuation-in-part of Ser. No. 08/740,653, filed Oct. 31, 1996, which is still pending, which is a divisional of Ser. No. 08/350,588, filed Jan. 30, 1995, now U.S. Pat. No. 5,578,292, which is a divisional of Ser. No. 07/991,237, filed Dec. 16, 1992, now U.S. Pat. No. 5,413,774, which originated from EP 92810046.0, filed Jan. 24, 1992. All of the aforementioned applications are hereby incorporated by reference herein in their entirety.

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         (c) 1999 The Gale Group
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S1        582   VACCIN?/TI AND (FAIL? OR INEFFECT? OR DISAPPOINT? OR INCON-
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              VIRUS?)/TI
S2        353   RD (unique items)
S3          9   S2 AND (SUPPOSITORY? OR UROGENTIAL? OR GENITOURIN? OR URIN-
              ARY? OR VAGINA? OR RECTAL? OR ENTRAL?)
S4        157   S2 AND FAIL?
S5          4   S4 AND WHOLE?
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☐	L8	L5 same (supposit$ or composition or vaccine or insertion or application or applying).ti,ab,clm.	160

END OF SEARCH HISTORY

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2. 20050096296. 23 Jan 04. 05 May 05. Pharmaceutical compositions with synchronized solubilizer release. Fikstad, David, et al. 514/58; 514/369 514/423 514/458 514/460 514/548 514/571 A61K031/724 A61K031/426 A61K031/401 A61K031/366.

3. 20040209807. 30 Jan 04. 21 Oct 04. Compositions and methods for enhanced mucosal delivery of Y2 receptor-binding peptides and methods for treating and preventing obesity. Quay, Steven C., et al. 514/12; 514/23 514/53 514/58 514/738 A61K038/22 A61K031/70 A61K031/7012 A61K031/724 A61K031/045.

4. 20030138491. 13 Aug 02. 24 Jul 03. Microencapsulation and sustained release of biologically active acid-stable or free sulfhydryl-containing proteins. Tracy, Mark A., et al. 424/486; 424/85.6 A61K038/21 A61K009/14.

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9. 6565888. 23 Aug 00; 20 May 03. Methods and compositions for the targeted delivery of biologically active agents. Tracy; Mark A., et al. 424/489; 424/130.1 424/184.1 424/204.1 424/234.1 424/237.1 424/244.1 424/422 424/426 424/490 424/491 424/493 424/497 424/499. A61K009/14.

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☐ 13. JP361225121A. 29 Mar 85. 06 Oct 86. PREVENTIVE FOR ASTHMA AND PREPARATION THEREOF. ABE, TORU, et al. A61K031/41; A61K009/00 A61K009/14 A61K009/16 A61K009/20 A61K009/48 A61K009/70 A61K047/00 C07D257/04.

"PATNO_JP356150015A" 14. JP 56150015A. Antiallergic agents - esp. effective in treating slow reacting substances of anaphylaxis. A61K031/12 C07C069/95.

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PUB-NO: JP361225121A
DOCUMENT-IDENTIFIER: JP 61225121 A
TITLE: PREVENTIVE FOR ASTHMA AND PREPARATION THEREOF

PUBN-DATE: October 6, 1986

INVENTOR-INFORMATION:

NAME	COUNTRY
ABE, TORU	
YANAGIHARA, YUKIYOSHI	
SHINODA, TAKAO	
KONO, SHIGEKATSU	
OHATA, KATSUYA	
OGASAWARA, YOSHIAKI	
KAGEYAMA, SHINJI	
OGUMA, TORU	
TSURITANI, MASAHIRO	
KURODA, TOSHIO	
HASHIMOTO, MITSUMASA	

ASSIGNEE-INFORMATION:

NAME	COUNTRY
WAKAMOTO PHARMACEUT CO LTD	

APPL-NO: JP60063320
APPL-DATE: March 29, 1985

INT-CL (IPC): A61K 31/41; A61K 9/00; A61K 9/14; A61K 9/16; A61K 9/20; A61K 9/48; A61K 9/70; A61K 47/00; C07D 257/04

ABSTRACT:

PURPOSE: To provide a preventive for asthma, containing a tetrazole derivative as an active component in an amount sufficient to exhibit the effect to suppress the isolation of SRS-A.

CONSTITUTION: 5-(3-n-Butyloxalylaminophenyl)tetrazole (abbreviated as MTB) of formula is used as an active component in an amount to exhibit the effect to suppress the isolation of SRS-A. It is mixed uniformly with one or more components selected from polysorbate 80, polyvinyl pyrrolidone, polyethylene glycol, hydroxypropylcellulose and hydroxypropylmethylcellulose to improve the bioavailability of MTB in the presence of a non-aqueous solvent,and the non-aqueous solvent is removed. As an alternative method, MTB is dissolved in liquid PEG and used as an active component of the titled agent optionally after diluting with an inert carrier. It is administered in the form of oral drug such as tablet, granule, etc., or inhalant, suppository, poultice, etc. It is administered at a dose of 10～500mg per head.

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　昭61-225121

⑤1Int.Cl.⁴	識別記号	庁内整理番号	④3公開　昭和61年(1986)10月6日
A 61 K 31/41	ACD		
9/00			
9/14			※審査請求　未請求　発明の数 2　（全8頁）

⑤4発明の名称　喘息予防剤及びその製剤法

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明　細　書

1. 発明の名称

喘息予防剤及びその製剤法

2. 特許請求の範囲

(1) ＳＲＳ－Ａ遊離抑制効果を奏する量の5－（3－n－ブチルオキサリルアミノフェニル）テトラゾールを有効成分として含有することを特徴とする喘息予防剤。

(2) ＳＲＳ－Ａ遊離抑制効果を奏する量の5－（3－n－ブチルオキサリルアミノフェニル）テトラゾールをポリソルベート80，ポリビニルピロリドン，ポリオキシエチレン硬化ヒマシ油，ポリエチレングリコール，ヒドロキシメチルセルロース，ヒドロキシプロピルセルロース及びヒドロキシプロピルメチルセルロースの群から選ばれる分散剤の1種又は2種以上と非水溶媒の共存下均一に混合した後非水溶媒を除去するか又は液状ポリエチレングリコールに溶解した状態で有効成分として含有させることを特徴とする喘息予防剤の製剤法。

3. 発明の詳細な説明

(1) 発明の目的

（産業上の利用分野）

本発明は，喘息予防剤及びその製剤法に関するものである。更に詳しくは，本発明はＳＲＳ－Ａ遊離抑制効果を奏する量の5－（3－n－ブチルオキサリルアミノフェニル）テトラゾール（以下ＭＴＢという）を有効成分として含有することを特徴とする喘息予防剤を提供するものである。ＭＴＢは非常に優れたＳＲＳ－Ａ遊離抑制作用とヒスタミン遊離抑制作用を兼備していることから，これを喘息患者に投与すれば，喘息惹起の原因物質である上記両成分の遊離が効果的に抑制され，喘息予防剤としての優れた効果を奏するものである。

（従来の技術）

喘息は発作性の呼吸困難と喘鳴を示す疾患で，気道狭窄によって起こるものである。

気道狭窄の原因としては，気道平滑筋の収縮，気道粘膜の浮腫，気道分泌の亢進，気道内の粘液栓の形成などが挙げられるが，最も重要なのは，気道平滑筋の収縮である。

喘息患者は一般的に気道が過敏であり，吸入アレルゲンを含めて多くの抗原に対してIgE抗体を産生し易く，体内にIgE抗体を多量保有しているため，花粉その他のアレルゲン（抗原）を吸入した場合，気道粘膜下組織に豊富に存在する肥満細胞の表面で抗原抗体反応が起こり易く，その反応を引金として遊離されるヒスタミン及びＳＲＳ－Ａによって，平滑筋収縮を始めとする喘息諸症状を引起こすものである。〔例ライフ・サイエンス発行；プログレス・イン・メディシン（Progress in Medicine）第３巻第655－666頁（1983年）.〕

ヒスタミンによる気管支平滑筋の収縮は非

常に敏感，即時的，強力であるが，その重篤な発作は通常~~2～3分程度の~~比較的短時間でおさまる。

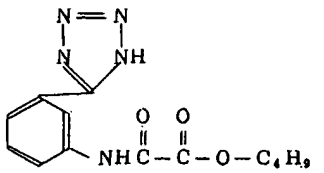
（アレルギー第７巻93－104頁，1958年）

これに対し，ＳＲＳ－Ａによる気管支平滑筋の収縮は，ゆっくり起こるが強力且つ長時間持続し，喘息患者に堪えられない多大の苦痛を与えるため，このＳＲＳ－Ａの遊離を効果的に抑制する薬剤の開発が待望されているところである。〔プログレス・イン・メディシン第３巻655－666頁（1983）.〕

ＳＲＳ－Ａ（Slow reacting substance of anaphylaxis）はIgE抗体の関与する抗原抗体反応により肥満細胞等より遊離されるが，ヒスタミン（preformed mediator に属する）と異なり，その反応の刺激で合成されるもの（newly generated mediator に属する）であり，アラキドン酸から５－リポキシゲナーゼにより開始される一連の反応により生成されるロイコトリエンC_4，D_4，E_4（LTC_4，LTD_4，LTE_4）がその

本体であり，それらの化学構造も明らかにされている。（免疫薬理第２巻第２号207－213頁，1984年.）

ＭＴＢは本出願人会社の研究部に於いて合成され，抗アレルギー作用を示すことが見出された化合物である。（特開昭57－11975号）



ＭＴＢがヒスタミンの遊離を抑制し，抗アレルギー作用を有することはすでに公知であるが，ＳＲＳ－Ａの遊離抑制作用については全く知られていなかった。〔ジャパニーズ・ジャーナル・オブ・ファーマコロジー（Japanese Journal of Pharmacology）第32巻689－697頁，1982年〕

（発明が解決しようとする問題点）

本発明者等は，抗喘息剤の開発を目的とし，

喘息症状を悪化させる最も重要な原因物質がＳＲＳ－Ａであることに着目し，ＳＲＳ－Ａの遊離を効果的に抑制する化合物の探索のため種々スクリーニング試験を行ない，ＭＴＢがその目的に合致する化合物であることを見出した。

次いで，ＭＴＢの医薬品としての製剤改良研究を行ない，ＭＴＢ原末が水に難溶性の化合物であり，製剤加工の際非常に取扱いにくく，原末をそのまま通常の方法で製剤化した場合は製剤の崩解性及び溶出性が悪く，有効成分の生体内利用率も不充分であることが分ったので，それらの問題点を解決するため種々検討を行なった結果，このたび喘息予防剤及びその製剤法の発明を完成したものである。

(2) 発明の構成

（問題点を解決するための手段）

本発明は「ＳＲＳ－Ａ遊離抑制効果を奏する量のＭＴＢを有効成分として含有することを特徴とする喘息予防剤（以下本製剤という）

及びその製剤法」に関するものである。

本薬剤は，通常，錠剤，顆粒剤，散剤，カプセル剤等の経口投与剤として使用されるが，吸入剤，坐剤，パップ剤，注射剤等としても使用出来る。

本薬剤は，通常，成人1回当り約10～500㎎，好ましくは50～300㎎の割合で，投与することにより優れた喘息予防効果が期待されるものである。

本薬剤を製造するに当り，慣用の製剤処方を採用することも出来るが，生体内利用率（Bioavoilability）を高めるため，ＭＴＢをポリソルベート80，ポリビニルピロリドン（以下ＰＶＰという），ポリオキシエチレン硬化ヒマシ油，ポリエチレングリコール（以下PEGという），ヒドロシメチルセルロース，ヒドロキシプロピルセルロース及びヒドロキシプロピルメチルセルロースの群から選ばれる成分（以下特定分散剤ということがある）の1種又は2種以上と非水溶媒の共存下均一に混

ロース，コーンスターチ，マンニット，軽質無水ケイ酸，カオリン等が使用出来る。

新製剤法によれば，有効成分ＭＴＢが特定分散剤と共に非水溶媒に溶解又は分散された後，溶媒蒸発と共に固溶体を形成するか又は共同沈殿を生じあるいは特定分散剤が液状のＰＥＧの場合はこれにＭＴＢが溶解した状態の製剤が提供され，分散性及び溶出性の著しく優れた生体内利用率の高い本薬剤を製造することが出来る。

示差熱走査熱量測定装置（ＤＳＣ30型，島津製作所製）による測定で，ＭＴＢは結晶性を示す吸収のピークを示したが，特定分散剤と共に非水溶媒共存下混合処理した物はピークを示さなかったことから，新製剤法に於ける非水溶媒処理は単に混合効率を高めるのみでなく，ＭＴＢの結晶構造自体に変化を起こすことが認められた。

又，この新製剤法に於いて，担体を使用せず又は制限して使用してＭＴＢを高濃度に含

合した後非水溶媒を除去するか，又は液状ＰＥＧに溶解した状態で有効成分として含有させ，必要に応じ医薬品として許容される不活性担体で稀釈して製剤化するのが好ましい。この方法（以下新製剤法という）に利用する不活性溶媒はＭＴＢと特定分散剤の両成分を同時に溶解又は分散するもので且つ蒸発除去の容易なものであれば特に限定しないが，通常メタノール，エタノール，イソプロピルアルコール，アセトン，ジクロルメタン等を単独又は混合して使用する。

特定分散剤は水及び非水溶媒の両方に分散又は溶解する比較的高分子の成分からなり，その使用量は種類によりかなり相違するが，ＭＴＢ1重量部に対し，通常0.01～10重量部の範囲で適宜選択出来る。

ＰＥＧは平均分子量200～6000程度のものが好適に使用出来る。

不活性担体は医薬品として許容されるものであれば特に限定されないが，通常結晶セル

むプレミックスを調製し，このプレミックスを担体で稀釈して常法により任意の形態の製剤にすることが出来るし，前記特定分散剤を担体と兼用して多量に使用し製剤化することも出来る。

通常は，一般に用いられる担体，結合剤，甘味料その他補助物質を特定分散剤と共に同時に混合して非水溶媒を用いる湿式造粒法で顆粒剤，散剤，粉剤等を得，必要に応じこれらをカプセルに充填してカプセル剤とするか又は打錠して錠剤にするのが簡便である。

この場合，ＭＴＢ及び特定分散剤が非水溶媒によって完全には溶解されなかった場合でも，ＭＴＢ製剤の溶出性は予想外に高い値を示すものである。

実施例1.

ＭＴＢ50㎎，結晶セルロース44㎎，コーンスターチ10㎎及び低置換ヒドロキシプロピルセルロース10㎎を混和し，これにＰＶＰ６㎎をイソ

プロピルアルコール30mlに溶解して添加し，均一に混合した後造粒し，40℃，5時間乾燥後整粒して細粒剤を得る。

実施例2.

ＰＶＰ６ｇの代りにＰＶＰ４ｇとポリソルベート－80　２ｇを使用した外は実施例１と同様にして細粒剤を得，これをゼラチン硬カプセルに充填してカプセル剤を得る。

実施例3.

ＭＴＢ100ｇをアセトン500mlに溶解し，これにポリソルベート－80　10ｇを加えて撹拌混合後，この溶液に結晶セルロース400ｇ，低置換度ヒドロキシプロピルセルロース50ｇ及びコーンスターチ440ｇを添加し，均一に混合した後，50℃で５時間乾燥後整粒して散剤を得る。

実施例4.

ＭＴＢ100ｇ，結晶セルロース420ｇ，コーンスターチ400ｇ及び低置換度ヒドロキシプロピルセルロース30ｇを混合した後，ＰＶＰ50ｇをイソプロピルアルコール550mlに溶解して加え，練合して0.7mmφスクリーンを使って押し出し顆粒状とし，50℃で５時間乾燥後整粒して500mg中50mgのＭＴＢを含有する顆粒剤を得る。

実施例5.

ＭＴＢ10ｇとヒドロキシプロピルメチルセルロース20ｇをジクロルメタン・エタノール等量混液200mlに加え，溶解後軽質無水ケイ酸20ｇを添加して均一に混合し，減圧下溶媒留去乾燥して40メッシュの篩を通過させた後，マンニット50ｇを添加して均一に混合し散剤を得る。

実施例6.

ＭＴＢ100ｇをジクロルメタン・エタノール等量混合液300mlに溶解し，これにポリソルベート－80　３ｇを加えて溶解し，次いで結晶セルロース167ｇを添加して均一に混合後，50℃

で４時間乾燥して粉末化する。これにステアリン酸マグネシウム４ｇを加えて均一に混合し，この混合粉末を４号カプセルに137mg宛充填して，１カプセル中ＭＴＢ50mgを含む硬カプセル剤を得る。

実施例7.

ＭＴＢ100ｇを平均分子量400のＰＥＧ400ｇに溶解し，これに軽質無水ケイ酸200ｇ及びカルボキシメチルセルロースカルシウム300ｇを混合して粉末とする。これを42メッシュの篩を通過させて500mg中ＭＴＢ50mg含有の散剤を得る。

実施例8.

ＭＴＢ100ｇ，結晶セルロース80ｇ，コーンスターチ20ｇ及び低置換度ヒドロキシプロピルセルロース16ｇを混合し，これにＰＶＰ16ｇ及びポリオキシエチレン硬化ヒマシ油４ｇをエタノール120mlに溶解して添加し，均一に混練した後造粒を行い，これを50℃４時間乾燥し，整粒後タルク４ｇを加えて均一に混合し，120mg宛４号カプセルに充填して１カプセル中ＭＴＢ50mgを含む硬カプセル剤を得る。

実施例9.

ＭＴＢ100ｇ及び平均分子量6000のＰＥＧ80ｇをジクロルメタン・エタノール等量混合液500mlに溶解し，これに軽質無水ケイ酸20ｇを加え混合後50℃で４時間乾燥後粉砕し，次いで結晶セルロース88ｇ，カルボキシメチルセルロース10ｇ及びステアリン酸マグネシウム２ｇを加え，常法により打錠して１錠中ＭＴＢ約50mg含有する錠剤を得る。

実施例10.

ＭＴＢ100ｇ，結晶セルロース80ｇ，コーンスターチ36ｇ及び低置換度ヒドロキシプロピルセルロース10ｇを混合し，これにＰＶＰ10ｇ及びポリソルベート－80　２ｇをエタノール120

mlに溶解して添加し，均一に練合後，0.7mmφスクリーンで押し出し顆粒状とし，50℃で5時間乾燥後整粒し，ステアリン酸マグネシウム2gを加えた後，常法により打錠して直径7mm，重量120mgの錠剤を得る。

実施例11.

MTB2gをアセトン10gに溶解し，これにポリソルベート－80 0.2gを加えて撹拌混合し，この溶液をカオリン511.8gと均一に混和後乾燥して乾燥粉末を得る。一方，グリセリン440gを100℃に加熱して水分を除き，これにホウ酸45gを加えて溶解し，これに上記乾燥粉末を混和し，冷後チモール0.5gを0.5gのハッカ油に溶解して添加し，よく混和してパップ剤を得る。

(3) 発明の効果

本薬剤は，喘息発作の引金となるヒスタミン及びSRS－Aの遊離抑制作用が非常に高く，又喘息発作時の気道狭窄（呼吸量低下）

(05)

（Ro：対照（未処置）群の遊離量
R：供試薬剤処置群の遊離量）

供試薬剤は本発明薬剤のMTBと比較薬剤のクロモグリク酸ナトリウム（以下DSCGという）及びトラニラスト（以下N－5′という）を用い，濃度10^{-8}～10^{-4}（g/ml）の範囲で試験した。なお，ヒスタミンの測定はジャーナル・オブ・アレルギー（Journal of Allergy）第46巻12～20頁，1970年に記載のメイ・シー・ディー等（May, C.D. et al）の方法に準じ，螢光法により行った。SRS－Aの測定は，薬物学実験（高木敬次郎，小澤光共著，南山堂発行）に記載のマグナス（Magnus）法により行った。

試験結果

本試験の成績は第1表に示す通りである。

各測定値は3回の平均値で示した。

(07)

の予防効果も非常に優れた喘息の予防薬である。

以下，本薬剤の効果を試験例により詳細に説明する。

試験例1.

（モルモット肺切片からのヒスタミン及びSRS－Aの遊離に及ぼすMTBの抑制効果試験）

試験方法

ハートレイ（Hartley）系雄性モルモットに抗BSAモルモット血清（0.5ml/頭）を静脈内投与して受動的に感作した。2日後，放血致死させて得られた肺を切片とした後，所定濃度の供試薬剤で処置し，5分間経過後抗原を作用させて遊離したヒスタミン及びSRS－Aの量を測定し，対照群（薬剤処置しなかった群）の遊離量と比較して遊離抑制率(%)を算出した。

$$遊離抑制率 = \frac{Ro - R}{Ro} \times 100\ (\%)$$

(08)

第　1　表

薬剤濃度 (g/ml)	遊離抑制率 (%) ヒスタミン			SRS－A		
	MTB	DSCG	N－5′	MTB	DSCG	N－5′
10^{-4}	37	2	16	64	13	54
10^{-5}	30	0	5	66	9	11
10^{-6}	14			49		
10^{-7}	6			28		
10^{-8}	8			2		
対照	0	0	0	0	0	0

第1表の成績から明らかなように，本発明薬剤MTBは公知のDSCG及びN－5′に比較してヒスタミン及びSRS－Aの遊離抑制率が著しく高く，特にSRS－A遊離抑制率は10^{-6}～10^{-4}（g/ml）の濃度に於いて49～66%と高い値を示した。

試験例 2.

（アカゲザル肺切片からのヒスタミン及びSRS－Aの遊離に及ぼすMTBの抑制効果試験）

試験方法

アカゲザルの肺を切片とした後，ヒト・アトピー性血清で受動的に感作を行い，以後試験例1と同様な方法で試験し，本発明薬剤 MTBのヒスタミン及びSRS－A遊離抑制効果を公知の薬剤DSCGと比較した。

試験結果

第2表に示す通りである。各測定値は3回の平均値で示した。

第 2 表

供試薬剤濃度 (g/ml)	抑制率 (%) ヒスタミン MTB	ヒスタミン DSCG	SRS－A MTB	SRS－A DSCG
10^{-4}	27	0	16	2
10^{-5}	2	0	17	0
10^{-6}	12		18	
10^{-7}	0		0	
対照	0	0	0	0

(19)

第 3 表

供試薬剤濃度 (g/ml)	遊離抑制率 (%) ヒスタミン MTB	ヒスタミン DSCG	ヒスタミン N−5′	SRS－A MTB	SRS－A DSCG	SRS－A N−5′
10^{-4}	27	18	31	47	39	37
10^{-5}	23	13	16	47	41	32
10^{-6}	23			43		
10^{-7}	8			31		
10^{-8}	0			2		
対照	0	0		0	0	0

試験例 4.　（実験的喘息の予防効果試験）

試験方法

モルモット抗DNP－AS血清で受動的に感作したモルモットを気密性の箱に入れ，無麻酔，無拘束下，ネブライザーを介して2.5mg/mlのDNP－BSAを15秒間吸入させ実験的喘息を惹起させた。モルモット胸郭部の変動を差圧トランデューサーを介してレコーダーに記録し，

(20)

試験例 3.

（ヒト肺切片からのヒスタミン及びSRS－Aの遊離に及ぼすMTBの抑制効果試験）

試験方法

肺癌手術により切除されたヒト肺の，肉眼的正常部をアカゲザルの場合に準じてヒト・アトピー性血清で受動的に感作し，以後試験例1と同様にして，供試薬剤のヒスタミン及びSRS－Aの遊離抑制効果を測定した。

試験結果

本試験の結果は第3表に示す通りである。各測定値は3回の平均値で示した。

(20)

1回当りの呼気量（ticlal volume）を経時的に測定し，喘息惹起前の値と比較して呼気量低下率を求めた。

供試薬剤は，MTBとN－5′を使用し，それぞれ250mg/Kgの割合で，喘息惹起の60分前に経口投与した。

試験結果

本試験の結果は，第4表に示す通りである。各測定値は7回の平均値で示した。

第 4 表

時間 (分)	呼気量低下率 (%) 対照	MTB	N－5′
0	0	0	0
1	34	17	26
2	48	17	24
3	47	21	24
4	46	23	26
5	42	21	23
6	41	22	25
8	39	21	28
10	34	21	24
15	30	14	27
20	25	19	22
30	29	15	19

(22)

第4表の成績から明らかなように，本発明薬剤ＭＴＢ投与群は薬剤を投与しない対照群及び比較薬剤Ｎ－5′投与群のいづれと比較しても，1回呼気量の低下が非常に少なく，特に，喘息惹起直後の急激な呼気量低下に対する抑制効果が優れていた。

ＭＴＢの温血動物に対する急性毒性は第5表に示す通りである。

第　5　表

急性毒性 LD_{50} (mg/Kg)					
投与経路 / 動物		i.v.	i.p.	s.c.	p.o.
マウス	雄	1130	1120	＞4000	＞4000
	雌	1225	1160	＞4000	＞4000
ラット	雄	1110	1430	＞4000	＞4000
	雌	1160	1430	＞4000	＞4000
犬	雄	−	−	−	＞4000
	雌	−	−	−	＞4000

(23)

試験結果

第6表に示す通り本発明薬剤は著しく高い溶出率を示した。

第　6　表

溶出率(%) / 時間(分)	硬カプセル剤		錠剤	
	本発明A	比較A	本発明B	比較B
5	77.6	3.6	51.2	2.1
10	87.8	6.2	60.0	3.7
20	98.0	12.3	84.3	6.8
30	99.8	17.6	93.6	9.5
40	101.4	22.5	97.8	10.9
60	98.7	31.7	98.4	12.0

本試験に使用した比較薬剤は下記の処方で調製した。

比較A

ＭＴＢ結晶粉末50gを乳糖68g及びステアリン酸マグネシウム2gと均一に混合し，120mgずつカプセルに充填し，1カプセル中ＭＴＢ

(25)

供試動物は次の通りである。

マウス：ddy,　体重　20～23g，1群20匹

ラット：wistar，体重110～130g，1群10匹

犬　：beagle，体重約8Kg，　1群3匹

次に新製剤法による本薬剤が著るしく高い溶出率及び生体内利用率（血中濃度）を示すことを説明するため，試験例を示す。

試験例5.　（溶出試験）

試験方法

溶出液として人工胃液（日本薬局方第1液）500mlを用い，液温37±0.5℃に保ち容器の底に供試薬剤（ＭＴＢ含量50mg）を入れパドルを100rpmで回転し，所定時間ごとに液をサンプリングし，経時的に液中に溶出されたＭＴＢ量を分光光度法により測定した。

供試薬剤

本発明A …… 実施例6の硬カプセル剤

本発明B …… 実施例10の錠剤

比　較A …… 常法による硬カプセル剤

比　較B …… 常法による錠剤

(24)

50mg含有する硬カプセル剤を得る。

比較B

ＭＴＢ結晶粉末50g，乳糖40g，コーンスターチ15g，結晶セルロース10g，デンプンのり3gを混合し，約40mlの水を加えて練合し，直径7mmのスクリーンより押し出し，顆粒状として乾燥後，整粒してステアリン酸マグネシウム2gを加えて打錠し，1錠中ＭＴＢ50mg含有する錠剤を得る。

試験例6.　（血中濃度測定試験）

試験方法

24時間絶食させた体重約10Kgの雄性ビーグル犬1群5頭に供試薬剤を経口投与した。薬剤投与後所定時間ごとに採血して，ＭＴＢの血中濃度を液体クロマトグラフィーにより測定した。

供試薬剤

試験例5と同じ。

試験結果

本試験の結果は第7表に示す通りである。

(26)

第　7　表

血中濃度(μg/ml) / 時間(分)	硬カプセル剤		錠剤	
	本発明A	比較A	本発明B	比較B
15	0.23	0.04	0.14	ND
30	0.36	0.08	0.28	0.03
45	0.44	0.12	0.39	0.05
60	0.57	0.14	0.56	0.07
90	0.62	0.30	0.64	0.13
120	0.47	0.18	0.56	0.09
180	0.23	0.08	0.31	0.04
240	0.16	0.05	0.22	0.03
360	0.09	0.03	0.10	ND

備考：1)　表中の成績は5頭の平均値で示した。

2)　NDは検出できなかったことを示す。

以上の各試験例から明らかなように，本発明によれば，非常に優れたSRS－A遊離抑制効果を奏する喘息予防剤を製造し得るものである。

特許出願人

わかもと製薬株式会社

(27)

第1頁の続き

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PGPUB-DOCUMENT-NUMBER: 20030138491
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030138491 A1

TITLE: Microencapsulation and sustained release of biologically active acid-stable or free sulfhydryl-containing proteins

PUBLICATION-DATE: July 24, 2003

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APPL-NO: 10/ 217953 [PALM]
DATE FILED: August 13, 2002

RELATED-US-APPL-DATA:
Application 10/217953 is a continuation-of US application 09/501934, filed February 10, 2000, US Patent No. 6465425

INT-CL: [07] A61 K 38/21, A61 K 9/14

US-CL-PUBLISHED: 424/486; 424/85.6
US-CL-CURRENT: 424/486; 424/85.6

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

This invention relates to sustained release compositions, and methods of forming and using said compositions, for the sustained release of biologically active acid-stable or free sulfhydryl-containing proteins, in particular .beta.-IFN. The sustained release composition of this invention comprises a biocompatible polymer having dispersed therein a stabilized biologically active acid-stable or free sulfhydryl-containing protein formulation and a nonionic polymer surfactant.

The method of the invention, for forming a composition for the sustained release of biologically active acid-stable or free sulfhydryl-containing protein, in particular .beta.-IFN, includes dissolving a polymer in a polymer solvent to form a polymer solution, adding a stabilized biologically active acid-stable or

free sulfhydryl-containing protein formulation and a nonionic surfactant to the polymer solution, and then solidifying the polymer to form a polymer matrix containing the stabilized biologically active acid-stable or free sulfhydryl-containing protein formulation, and a nonionic surfactant.

The method of using the sustained release composition of the present invention comprises providing a therapeutically effective blood level of biologically active acid-stable or free sulfhydryl-containing protein in a subject for a sustained period by administering to the subject a dose of the sustained release composition described herein.

RELATED APPLICATION

[0001] This application is a continuation of U.S. application Ser. No. 09/501,934, filed Feb. 10, 2000. The entire teachings of the above application are incorporated herein by reference.

DOCUMENT-IDENTIFIER: US 20030138491 A1
TITLE: Microencapsulation and sustained release of biologically active acid-stable or free sulfhydryl-containing proteins

Detail Description Paragraph:
[0059] The composition of this invention can be administered to a human, or other animal, by injection, implantation (e.g., subcutaneously, intramuscularly, intraperitoneally, intracranially, and intradermally), administration to mucosal membranes (e.g., intranasally, intravaginally, intrapulmonary or by means of a suppository), or in situ delivery (e.g., by enema or aerosol spray) to provide the desired dosage of biologically active acid-stable or free sulfhydryl-containing protein, for example .beta.-IFN, based on the known parameters for treatment with such protein of the various medical conditions.

CLAIMS:

10. The sustained release composition of claim 1 wherein the surfactant is selected from the group consisting of: poloxamers, polysorbates, polyethyleneglycols, polyoxyethlene fatty acid esters, bile salts, benzalkonium chloride, polyoxyethylene (40) monostearate and combinations thereof.

21. The sustained release composition of claim 20 wherein the nonionic surfactant is selected from the group consisting of: poloxamers, polysorbates, polyethyleneglycol, polyoxyethlene fatty acid esters and combinations thereof.

PGPUB-DOCUMENT-NUMBER: 20020032171
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020032171 A1

TITLE: Clear oil-containing pharmaceutical compositions containing a therapeutic agent

PUBLICATION-DATE: March 14, 2002

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APPL-NO: 09/ 877541 [PALM]
DATE FILED: June 8, 2001

RELATED-US-APPL-DATA:
Application 09/877541 is a continuation-in-part-of US application 09/345615, filed June 30, 1999, US Patent No. 6267985
Application 09/877541 is a continuation-in-part-of US application 09/751968, filed December 29, 2000, PENDING
Application 09/751968 is a continuation-in-part-of US application 09/375636, filed August 17, 1999, US Patent No. 6309663

INT-CL: [07] A61 K 31/715, A61 K 35/78

US-CL-PUBLISHED: 514/54; 424/727, 424/731, 424/750, 424/757
US-CL-CURRENT: 514/54; 424/727, 424/731, 424/750, 424/757

ABSTRACT:

The present invention relates to pharmaceutical compositions and methods for improved solubilization of triglycerides and improved delivery of therapeutic agents. Compositions of the present invention include a carrier, where the carrier is formed from a combination of a triglyceride and at least two surfactants, at least one of which is hydrophilic. Upon dilution with an aqueous medium, the carrier forms a clear, aqueous dispersion of the triglyceride and surfactants.

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/345,615, filed Jun. 30, 1999, and a continuation-in-part of U.S. application Ser. No. 09/751,968, filed Dec. 29, 2000, which is a continuation-in-part of U.S. application Ser. No. 09/375,636, filed Aug. 17, 1999, the disclosures of which are hereby incorporated by reference.

DOCUMENT-IDENTIFIER: US 20020032171 A1
TITLE: Clear oil-containing pharmaceutical compositions containing a therapeutic agent

Summary of Invention Paragraph:
[0024] In another embodiment, the present invention relates to dosage forms comprising the pharmaceutical compositions described herein. The dosage forms may be processed by techniques selected from the group consisting of lyophilization, encapsulation, extruding, compression, melting, molding, spraying, coating, comminution, mixing, homogenization, sonciation, granulation, and combinations thereof. Dosage forms include, but are not limited, those selected from the group consisting of pills, capsules, caplets, tablets, granules, beads, powders, solutions, suspensions, emulsions, creams, ointments, lotions, suppositories, sprays, aerosols, pastes, gels, drops, douches, ovules, wafers, troches, cachets, syrups and elixirs.

Detail Description Paragraph:
[0193] Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, buccal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, as well as for oral administration. Thus, the dosage form can be a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup, elixir, or other dosage form, as desired. If formulated as a suspension, the composition can further be processed in capsule form.

CLAIMS:

14. The pharmaceutical composition of claim 6, wherein the hydrophilic surfactant is selected from the group consisting of PEG- 10 laurate, PEG- 12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG- 15 stearate, PEG-3 2 distearate, PEG-40 stearate, PEG- 100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE- 10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG- 100 succinate, PEG-24 cholesterol, polyglyceryl- 10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, and mixtures thereof.

15. The pharmaceutical composition of claim 6, wherein the hydrophilic surfactant is selected from the group consisting of PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, and mixtures thereof.

16. The pharmaceutical composition of claim 6, wherein the hydrophilic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, and mixtures

thereof.

77. A dosage form comprising the pharmaceutical composition of claim 1, wherein the dosage form is selected from the group consisting of a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup and elixir.

101. The pharmaceutical composition of claim 93, wherein the hydrophilic surfactant is selected from the group consisting of PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG- 15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 capratelcaprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG- 100 succinate, PEG-24 cholesterol, polyglyceryl- 10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, and mixtures thereof.

102. The pharmaceutical composition of claim 93, wherein the hydrophilic surfactant is selected from the group consisting of PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, and mixtures thereof.

103. The pharmaceutical composition of claim 93, wherein the hydrophilic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, and mixtures thereof.

157. A dosage form comprising the pharmaceutical composition of claim 88, wherein the dosage form is selected from the group consisting of a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup and elixir.

179. The method of claim 164, wherein the dosage form is selected from the group consisting of a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup and elixir.

First Hit Fwd Refs

L2: Entry 8 of 14 File: USPT Jul 13, 2004

DOCUMENT-IDENTIFIER: US 6761903 B2
TITLE: Clear oil-containing pharmaceutical compositions containing a therapeutic agent

Brief Summary Text (26):
In another embodiment, the present invention relates to dosage forms comprising the pharmaceutical compositions described herein. The dosage forms may be processed by techniques selected from the group consisting of lyophilization, encapsulation, extruding, compression, melting, molding, spraying, coating, comminution, mixing, homogenization, sonciation, granulation, and combinations thereof. Dosage forms include, but are not limited, those selected from the group consisting of pills, capsules, caplets, tablets, granules, beads, powders, solutions, suspensions, emulsions, creams, ointments, lotions, suppositories, sprays, aerosols, pastes, gels, drops, douches, ovules, wafers, troches, cachets, syrups and elixirs.

Detailed Description Text (155):
Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, buccal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, as well as for oral administration. Thus, the dosage form can be a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup, elixir, or other dosage form, as desired. If formulated as a suspension, the composition can further be processed in capsule form.

CLAIMS:

14. The pharmaceutical composition of claim 6, wherein the hydrophilic surfactant is selected from the group consisting of PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, and mixtures thereof.

15. The pharmaceutical composition of claim 6, wherein the hydrophilic surfactant is selected from the group consisting of PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20,

polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, and mixtures thereof.

16. The pharmaceutical composition of claim 6, wherein the hydrophilic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, and mixtures thereof.

77. A dosage form comprising the pharmaceutical composition of claim 1, wherein the dosage form is selected from the group consisting of a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup and elixir.

103. The method of claim 88, wherein the dosage form is selected from the group consisting of a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup and elixir.

US-PAT-NO: 6465425
DOCUMENT-IDENTIFIER: US 6465425 B1

TITLE: Microencapsulation and sustained release of biologically active acid-stable or free sulfhydryl-containing proteins

DATE-ISSUED: October 15, 2002

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ASSIGNEE-INFORMATION:

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APPL-NO: 09/ 501934 [PALM]
DATE FILED: February 10, 2000

INT-CL: [07] A01 N 37/18

US-CL-ISSUED: 514/2; 514/1, 514/724
US-CL-CURRENT: 514/2; 514/1, 514/724

FIELD-OF-SEARCH: 514/1, 514/2, 514/724

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL | Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4252791	February 1981	Grossberg et al.	424/85
☐	4389330	June 1983	Tice et al.	427/213.36
☐	4462940	July 1984	Hanisch et al.	260/112R
☐	4711782	December 1987	Okada et al.	424/455
☐	4767628	August 1988	Hutchinson	424/426
☐	4818542	April 1989	DeLuca et al.	424/491
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☐	4871538	October 1989	Yim et al.	424/85.7

☐	4962091	October 1990	Eppstein et al.	514/2
☐	4992271	February 1991	Fernandes et al.	424/85.2
☐	5004605	April 1991	Hershenson et al.	424/85.6
☐	5019400	May 1991	Gombotz et al.	424/497
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☐	5176907	January 1993	Leong	424/78.08
☐	5316774	May 1994	Eury et al.	424/501
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☐	5594091	January 1997	Igari et al.	528/271
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0307097	August 1988	EP	
0330180	February 1989	EP	
2 620 621	March 1989	FR	
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WO 90/13780	November 1990	WO	
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Billiau, A., et al., "Human Fibroblast Interferon for Clinical Trials: Pharmacokinetics and Tolerability in Experimental Animals and Humans," Antimicrobial Agents and Chemotherapy, 16(1):56-63 (1979).

ART-UNIT: 1656

PRIMARY-EXAMINER: Riley; Jezia

ATTY-AGENT-FIRM: Hamilton, Brook, Smith and Reynolds, P.C.

ABSTRACT:

This invention relates to sustained release compositions, and methods of forming and using said compositions, for the sustained release of biologically active acid-stable or free sulfhydryl-containing proteins, in particular .beta.-IFN. The sustained release composition of this invention comprises a biocompatible polymer having dispersed therein a stabilized biologically active acid-stable or free sulfhydryl-containing protein formulation and a nonionic polymer surfactant.

53 Claims, 4 Drawing figures

DERWENT-ACC-NO: 1982-02787E
DERWENT-WEEK: 198202

TITLE: Antiallergic agents - esp. effective in treating slow reacting substances of anaphylaxis

PATENT-ASSIGNEE: TAKEDA CHEM IND LTD (TAKE)

PRIORITY-DATA: 1980JP-0053128 (April 21, 1980)

Search Selected | Search ALL | Clear

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 56150015 A	November 20, 1981		004	
JP 88051125 B	October 13, 1988		000	

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP 56150015A	April 21, 1980	1980JP-0053128	

INT-CL (IPC): A61K 31/12; C07C 69/95

ABSTRACTED-PUB-NO: JP 56150015A
BASIC-ABSTRACT:

Antiallergic agents contg. quinones of formula (I) are new (where n is 1-10; R1 is Me or MeOH, or two of them combined each other form -CH=CH-CH=CH-; R2 is H, lower alkyl or (CH2CH:C(Me)CH2) mH (where m is 1-10)). (I) are effective in prevention or treatment of allergic diseases caused by slow reacting substances of analphylaxis (SRS-A) (e.g. bronchial asthma, allergic rhinitis, uriticaria). (I) may be administered orally or parenterally (injection, external application, inhalation) at a dose of 0.1-10 mg/kg/adult a day. (I) may be formulated into capsules, granules, powders, tablets, troaches, pills, ointments, syrups, injections, suppositories, aerosols, or inhalations, together with various components such as excipient (e.g. sugar, lactose, glucose, starch, mannitol, sorbitol, cellulose, talc, cyclodextrin), binder (e.g. cellulose, methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, polyethylene glycol (PEG), sugar, starch), disintegrator (e.g. starch, CMC, CMC-Ca), lubricant (e.g. talc), preservative (e.g. Na benzoate, NaHSO3), suspending agent (e.g. methylcellulose, Al stearate), dispersing agent (e.g. Polysorbate 80, Emergen 408, Emerson 310), solvent (e.g. water), and base (e.g. cacao butter, PEG, Witepsol, vaseline.

ABSTRACTED-PUB-NO: JP 56150015A
EQUIVALENT-ABSTRACTS:

DERWENT-CLASS: A96 B05
CPI-CODES: A12-V01; B10-A06; B12-A07; B12-D02; B12-K02; B12-L04;

⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭56—150015

⑤Int. Cl.³	識別記号	庁内整理番号	㊸公開　昭和56年(1981)11月20日
A 61 K 31/12	ABF	6408—4C	

発明の数　1
審査請求　未請求

（全 4 頁）

⑤抗アレルギー剤

豊中市新千里南町２丁目26番３号

⑫発　明　者　渡辺正純
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⑪出　願　人　武田薬品工業株式会社
大阪市東区道修町２丁目27番地

⑭代　理　人　弁理士　松居祥二

㉑特　　願　昭55—53128
㉒出　　願　昭55(1980)４月21日

⑫発　明　者　牧良孝
京都市西京区大原野上里鳥見町５番地の17

⑫発　明　者　寺尾秦次

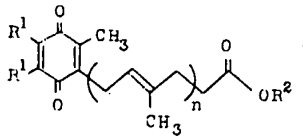
明　細　書

1. 発明の名称

抗アレルギー剤

2. 特許請求の範囲

式



〔式中、nは1から10までの整数を、R^1 はメチル基，メトキシ基または２つの R^1 で $-CH=CH-CH=CH-$ 基を示し、R^2 は水素原子，低級アルキル基または $+CH_2-CH=C(CH_3)-CH_2\rightarrow_m H$ 基（mは1から10までの整数）を示す〕で表わされる化合物を含有する抗アレルギー剤。

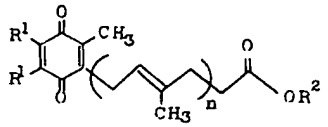
3. 発明の詳細な説明

本発明は新規抗アレルギー剤に関する。

一般にアレルギーに基づくと考えられる疾患は即時型と遅延型に分類され、前者は抗原抗体反応の結果生体局所に化学的伝達体が産生，放出され、この物質が気管支筋，肺静脈などの平滑筋を収縮したり皮膚血管の透過性を亢進するなど生体に障害をひきおこすと考えられている。このような化学的伝達体としてヒスタミンや多価不飽和脂肪酸（特にアラキドン酸）のリポキシゲネースによる代謝産物、たとえば slow reacting substance of anaphylaxis（以下SRS－Aと略す）などがあげられるが、SRS－Aによるアレルギー疾患に対し有効な化合物は現在広く検討段階にありその報告例は3-amino－1－〔m－(trifluoromethyl)-phenyl〕－2－phrazoline(BW－755Cと略す，FEBS Lett.，110巻，213－215頁，1980年），5，8，11，14－eicosatetraynoic acid（TYAと略す，Prostaglandins，14巻，21－38頁，1977年），baicalein phosphate disodium（BPSと略す，代謝，10巻，730－739頁(1973)）など極めて少ない。本発明者らは抗アレルギー剤として、なかでもSRS－Aの産生，放出を抑制する抗アレルギー剤の探索を進めてきた。その結

果、下式（Ⅰ）で表わされる化合物がＳＲＳ－Ａの産生，放出を極めて強力に抑制し、抗アレルギー剤として有用であることを見い出し、これに基づいて本発明を完成した。

すなわち、本発明は式



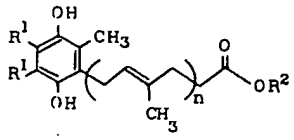
（Ⅰ）

〔式中、nは1から10までの整数を、R^1 はメチル基，メトキシ基または2つの R^1 で $-CH=CH-CH=CH-$ 基を示し、R^2 は水素原子，低級アルキル基または $+CH_2-CH=C(CH_3)-CH_2\rangle_m H$ 基（mは1から10までの整数）を示す）で表わされる化合物を含有する抗アレルギー剤である。

上記式（Ⅰ）に関し、R^2 で示される低級アルキル基としては、たとえば C_{1-4} アルキル基（例、メチル，エチル，プロピル，イソプロピル，ブチル，イソブチル，sec－ブチル，tert－ブチル基）があげられる。

上記化合物（Ⅰ）のなかでも R^1 がメトキシ基，R^2 が水素原子の化合物は上記薬理作用において優れており、キノン側鎖における炭素数が10～20の化合物が本発明の目的に特に適した化合物である。

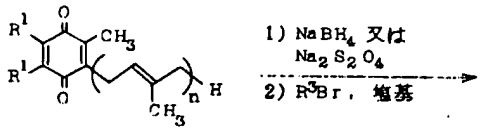
上記式（Ⅰ）で示されるキノン類は生体内では式

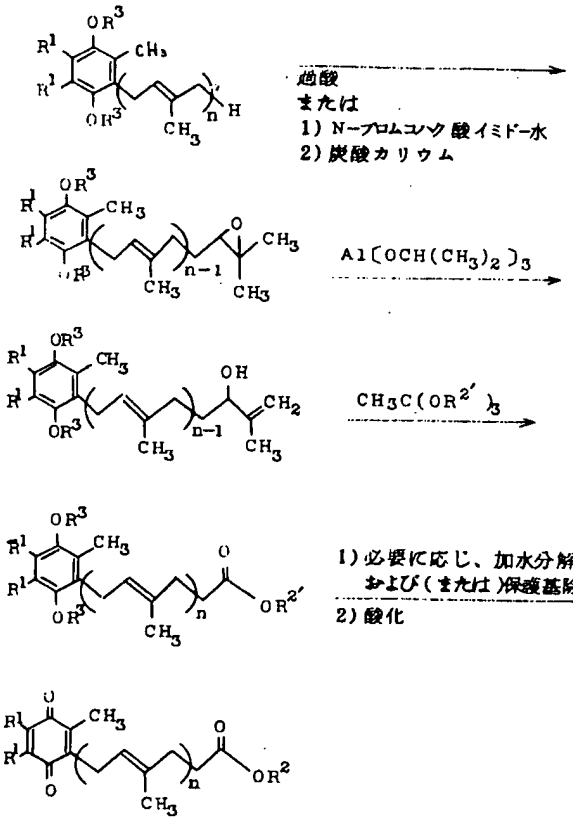


（Ⅰ′）

〔式中、R^1 ，R^2 およびnは前記と同意義〕で表わされるヒドロキノン類と相互変換しており、これらの化合物は生理学的意義において同等である。

化合物（Ⅰ）は、たとえば特願昭54－61915号に開示された方法またはそれらに準じて以下のように製造し得る。





（Ⅰ）

〔式中、R^3 は水酸基の保護基を、$R^{2'}$ は低級アルキル基を示し、他の記号は前記と同意義〕

化合物（Ⅰ）は前述のとおりＳＲＳ－Ａの産生，放出を極めて強力に抑制し、ＳＲＳ－Ａに起因する種々のアレルギー症（例、気管支喘息，アレルギー性鼻炎，じん麻疹）の治療，予防に有用である。

本発明の抗アレルギー剤は、その有効成分である式（Ⅰ）で示される化合物自体をそのまゝ投与することもできるが、一般には種々の医薬組成物として投与される。このような医薬組成物の剤形の例としては、例えばカプセル剤，顆粒剤，散剤，錠剤，トローチ剤，丸剤，軟膏剤，シロップ剤，注射剤，坐剤，エーロゾル剤，吸入剤等があげられる。

また医薬組成物に使用されるものとしては、例えば白糖，乳糖，ブドウ糖，でん粉，マンニット，ソルビット，セルロース，タルク，シクロデキストリン等の賦形剤、セルロース，メチルセルロース，ポリビニルピロリドン，ゼラチン，アラビヤ

ゴム，ポリエチレングリコール，白糖，でん粉等の結合剤、でん粉，カルボキシメチルセルロース，カルボキシメチルセルロースのカルシウム塩等の崩壊剤、タルク等の滑沢剤、安息香酸ナトリウム、亜硫酸水素ナトリウム等の保存剤、メチルセルロース，ステアリン酸アルミニウム等のけんだく化剤、ポリソルベート８０，エマルゲン４０８，エマゾール３１０等の分散剤、水等の溶剤、カカオ脂，ポリエチレングリコール，ウエテアゾール，白色ワセリン等の基剤等が挙げられ、これらは製剤の種類に応じて適宜選択される。

この発明の抗アレルギー剤は通常の抗アレルギー剤に準じて経口的または非経口的（例、注射，塗布，吸入等）に人間を含む哺乳動物に投与され、皮膚症状，喘息および鼻炎等のアレルギー症状等を効果的に抑制することができる。

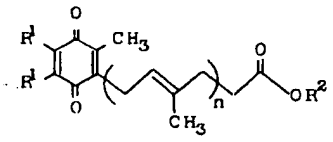
本発明の抗アレルギー剤の毒性は極めて低く、臨床的な投与量としては経口もしくは非経口のルートにより、成人１日当り化合物（Ⅰ）として約0.1－１０㎎／㎏程度が好んで用いられる。

実験例１

本発明の抗アレルギー剤のＳＲＳ－Ａ産生に対する抑制作用を Orange および Mooreの方法〔Ｊ．Immunol．，１１６巻，３９２頁(１９７６年)〕に従つて測定した。すなわち、抗原として卵白アルブミンを用いて感作したモルモット（Hartley 系雄 雄，体重３００～３５０ｇ）の肺切片に、化合物（Ⅰ）と抗原を同時に添加し、その際産生，放出されるＳＲＳ－Ａ量を Brocklehurst（J．physiol．，１５１巻４１６－４３５頁，１９６０年）の方法によつて測定した。その結果第一表に示すように本件化合物は低濃度においてＳＲＳ－Ａの産生，放出を強力に抑制し、その強度は前記公知化合物 ＢＷ－７５５Ｃ，ＴＹＡ，ＢＰＳなどに較べて顕著に優れていることが認められた。

第 一 表

ＳＲＳ－Ａの産生，放出に対する抑制作用



（Ⅰ）

化合物※）			濃度	抑制作用
R^1	R^2	n	(μM)	(%)※※）
CH_3O	H	2	1	35.0±6.3
CH_3O	H	3	1	21.8±8.5
	H	3	1	24.3±14.2
ＢＷ－７５５Ｃ			10	4.7±3.7
			100	15.3±4.3
ＴＹＡ			1	1.3±1.2
			10	56.9±5.9
ＢＰＳ			10	18.7±6.6
			100	50.8±10.7

※）化合物はエタノールまたはジメチルスルホキシド溶液として添加した。

※※）抗原抗体反応によるＳＲＳ－Ａの産生，放出の阻害率。

実施例１

カプセル剤

本発明化合物（Ⅰ式中 $R^1=CH_3O$，$R^2=H$，n＝３）	３０㎎
微結晶セルロース	３０㎎
乳糖	５７㎎
ステアリン酸マグネシウム	３㎎
全量	１２０㎎

上記成分を常法により混合したのちゼラチンカプセルに充填しカプセル剤とした。

実施例２

錠剤

本発明化合物（Ⅰ式中 $R^1=CH_3O$，$R^2=H$，n＝２）	３０㎎
乳糖	４４㎎
でん粉	１０.６㎎
でん粉（のり用）	５㎎
ステアリン酸マグネシウム	０.４㎎
カルボキシメチルセルロースカルシウム	２０㎎

全量　　110 mg

上記成分を常法により混合したのち錠剤とした。

実施例3

軟カプセル剤

本発明化合物（I式中 R^1 =  , R^2=H,
n=3）　　30 mg

トウモロコシ油　　110 mg

全量　　140 mg

上記成分を混合溶液としたのち常法により軟カプセル剤とした。

代理人　弁理士　松居祥二

First Hit Fwd Refs

L8: Entry 101 of 160 File: USPT Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968490 A
TITLE: Antiperspirant deodorant compositions

CLAIMS:

14. The composition of claim 2 wherein the nonionic surfactant comprises methyl gluceth-20, methyl gluceth-10, PEG-20 methyl glucose distearate, PEG-20 methyl glucose sesquistearate, PEG-200 castor oil, C.sub.11-15 pareth-20, ceteth-8, ceteth-12, dodoxynol-12, laureth-15, PEG-20 castor oil, polysorbate 20, steareth-20, polyoxyethylene-10 cetyl ether, polyoxyethylene-10 stearyl ether, polyoxyethylene-20 cetyl ether, polyoxyethylene-21 stearyl ether, polyoxyethylene-10 oleyl ether, polyoxyethylene-20 oleyl ether, an ethoxylated nonylphenol having at least 9 ethylene oxide moieties, an ethoxylated octylphenol having at least 9 ethylene oxide moieties, an ethoxylated dodecyl phenol having at least 9 ethylene oxide moieties, an ethoxylated fatty (C.sub.6 -C.sub.22) alcohol having at least 9 ethylene oxide moieties, polyoxyethylene-20 isohexadecyl ether, dimethicone copolyol, polyoxyethylene-23 glycerol laurate, polyoxyethylene-20 glyceryl stearate, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, a polyoxyethylene-20 sorbitan monoester, polyoxyethylene-80 castor oil, polyoxyethylene-15 tridecyl ether, polyoxyethylene-6 tridecyl ether, and mixtures thereof.

18. The composition of claim 16 wherein the first surfactant is selected from the group consisting of isoceteth-20, ceteth-20, dimethicone copolyol, an ethoxylated nonylphenol having at least 9 ethylene oxide moieties, an ethoxylated dodecylphenol having at least 9 ethylene oxide moieties, an ethoxylated octylphenol having at least 9 ethylene oxide moieties, steareth-10, PEG-20 glyceryl stearate, steareth-20, POE(6)tridecylether, PEG-80 castor oil, steareth-21, polysorbate 20, an ethoxylated fatty (C.sub.6 -C.sub.22) alcohol having at least 9 ethylene oxide moieties, and mixtures thereof.

First Hit Fwd Refs

L8: Entry 102 of 160 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5961997 A
TITLE: Antipruritic composition

CLAIMS:

1. A hypoallergenic, noncomedogenic, nonacnegenic, antipruritic composition which is oil-free, lanolin-free, fragrance-free, and free of Imidazolidinyl urea, quaternium-15, germall, the composition comprising about 0.5% to 1.5% menthol, about 0.5% to 1.5% camphor, about 0.5% to 1.0% phenol, about 1% to 10% lidocaine, about 1% to 2.5% pramoxine, about 10% to 50% distilled water, about 5% to 25% emulsifying wax NF, about 2% to 7% behenric acid, about 1% to 4% PEG 120 methylglucose dioleate, about 1% to 5% polysorbate 20, about 1% to 3% polysorbate 80, about 1% to 5% sorbitan sesquioleate, about 0.5% to 0.15% methyl paraben, about 0.3% to 0.10% propylparaben, about 1% to 5% C12-15 alkyl benzoate in a carrier containing only those ingredients rated 0 or 1 with respect to comedogenicity and irritancy.

First Hit Fwd Refs

L8: Entry 93 of 160 File: USPT Aug 6, 2002

DOCUMENT-IDENTIFIER: US 6428816 B1
TITLE: Carotenoid agent for inhibiting the conversion of epithelial cells to tumors

CLAIMS:

1. A method of inhibiting carcinogen-mediated conversion of melanocyte cells to melanomas, comprising the step of administering to the cells an anti-tumorigenic composition comprising: 0.1 to 10% by weight of a water insoluble carotenoid; and 90 to 99.9% by weight of a non-toxic carrier medium including a suspending agent selected from the group consisting of fatty acids, triglyceride lipids, non-saponifiable lipids, and combinations thereof; an emulsifier selected from the group consisting of a Tween polysorbate glycerol fatty acid esters and acetylated esters of fatty acids; and a water soluble dispersing agent which is a sugar or a polyol.

6. A method of protecting DNA against carcinogen-mediated damage thereby to inhibit conversion of melanocyte cells to melanoma, comprising the step of administering to the cells a composition comprising 0.1 to 10% by weight of a water insoluble carotenoid which includes .mu.-carotene; and 90 to 99.9% by weight of a non-toxic carrier medium including a suspending agent selected from the group consisting of fatty acids, triglyceride lipids, non-saponifiable lipid preparations, soluble hydrocarbons and combinations thereof; an emulsifier selected from the group consisting of a Tween polysorbate glycerol fatty acid esters and acetylated esters of fatty acids; and a water soluble dispersing agent which is a sugar or a polyol.

US-PAT-NO: 6428816
DOCUMENT-IDENTIFIER: US 6428816 B1

TITLE: Carotenoid agent for inhibiting the conversion of epithelial cells to tumors

DATE-ISSUED: August 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Meyskens, Jr.; Frank L.	Irvine	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Cognis Australia Pty., Ltd.	Broadmeadows			AU	03

APPL-NO: 08/ 718522 [PALM]
DATE FILED: January 16, 1997

PARENT-CASE:
This application is a continuation-in part of U.S. application Ser. No. 08/743,174, filed Nov. 5, 1996, now U.S. Pat. No. 6,132,790, which is a continuation of U.S. application Ser. No. 08/604,359, filed Feb. 21, 1996, now abandoned, which is a continuation of U.S. application Ser. No. 08/204,188, filed on Apr. 29, 1994, now abandoned, which is a 371 of PCT/AU92/00470 filed on Sep. 7, 1992. Benefit of these applications is claimed pursuant to 35 U.S.C. .sctn.120.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
AU	PM4931	October 8, 1994

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/AU95/00199	April 10, 1995	WO95/27483	Oct 19, 1995	Jan 16, 1997	Jan 16, 1997

INT-CL: [07] A61 K 35/78, A61 K 31/07

US-CL-ISSUED: 424/725; 424/773, 514/725, 514/938
US-CL-CURRENT: 424/725; 424/773, 514/725, 514/938

FIELD-OF-SEARCH: 424/195.1, 424/725, 424/773, 514/725, 514/938

PRIOR-ART-DISCLOSED:

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Search Selected | Search ALL | Clear

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☐	5705180	January 1998	Schlipalius	424/423
☐	6132790	October 2000	Schilpalius	426/540

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ART-UNIT: 1651

PRIMARY-EXAMINER: Tate; Christopher R.

ATTY-AGENT-FIRM: Drach; John E. Ettelman; Aaron R.

ABSTRACT:

A method of inhibiting carcinogen mediated conversion of melanocyte cells and protecting DNA against carcinogen-mediated damage by administering a composition comprising a water insoluble carotenoid such as beta-carotene is disclosed.

19 Claims, 18 Drawing figures

DOCUMENT-IDENTIFIER: US 20050020576 A1
TITLE: Kappa agonist compounds and pharmaceutical formulations thereof

Detail Description Paragraph:
[0665] The compositions are formulated as injectables, as oral and rectal formulations for systemic administration, and for local and topical administration as creams, aqueous or non-aqueous suspension, lotions, emulsions, suspensions or emulsions containing micronized particles, gels, foams aerosols, solids and other suitable vehicles for application to the skin, eyes, lips and mucosa, as suppositories or cream for vaginal administration, and as combinations with bandages, patches, bioadhesives and dressings. The compounds may be formulated in combination with other agents, such as local anesthetics and other therapeutic agents. The other agents may be mixed in the compositions are provided and administered prior to, simultaneously with or subsequent to administration of the compositions provided for the methods herein. Such agents include, but are not limited to: antibiotics, including cephalosporins, .beta.-lactams, tetracyclines, vancomycins, sulfas and aminoglycosides; antivirals, including acylovir; and antifungals including clotrimazole.

Detail Description Paragraph:
[0718] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (Tween 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

DOCUMENT-IDENTIFIER: US 20020012680 A1
TITLE: Compositions and methods for improved delivery of lipid regulating agents

Detail Description Paragraph:
[0137] Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, in the form of a triglyceride-free cream, lotion, ointment, suppository, gel or the like. If such a formulation is desired, other additives may be included, such as are well-known in the art, to impart the desired consistency and other properties to the formulation. The compositions of the present invention can also be formulated as a spray or an aerosol. In particular, the compositions may be formulated as a sprayable solution, and such formulation is particularly useful for spraying to coat a multiparticulate carrier, such as a bead. Such multiparticulate carriers are well known in the art.

CLAIMS:

13. The pharmaceutical composition of claim 5, wherein the hydrophilic surfactant is PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, or a mixture thereof.

14. The pharmaceutical composition of claim 5, wherein the hydrophilic surfactant is PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

15. The pharmaceutical composition of claim 5, wherein the hydrophilic surfactant is PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, or a mixture thereof.

67. A dosage form comprising the pharmaceutical composition of claim 1 formulated as a solution, a cream, a lotion, an ointment, a suppository, a spray, an aerosol, a paste or a gel.

83. The pharmaceutical composition of claim 75, wherein the hydrophilic surfactant is PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate,

PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, or a mixture thereof.

84. The pharmaceutical composition of claim 75, wherein the hydrophilic surfactant is PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

85. The pharmaceutical composition of claim 75, wherein the hydrophilic surfactant is PEG-35 castor oil, PEG40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, or a mixture thereof.

137. The method of claim 136, wherein the dosage form is a capsule, a cream, a lotion, an ointment, a suppository, a paste or a gel.

US 20020012680A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0012680 A1**

Patel et al. (43) **Pub. Date: Jan. 31, 2002**

(54) **COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF LIPID REGULATING AGENTS**

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(21) Appl. No.: **09/898,553**

(22) Filed: **Jul. 2, 2001**

Related U.S. Application Data

(63) Continuation of application No. 09/258,654, filed on Feb. 26, 1999, now Pat. No. 6,294,192.

Publication Classification

(51) **Int. Cl.**[7] **A61K 9/00**

(52) **U.S. Cl.** **424/400**

(57) **ABSTRACT**

The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.

1003
10/224(2) ?

PGPUB-DOCUMENT-NUMBER: 20030044434
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030044434 A1

TITLE: Self-emulsifying formulation for lipophilic compounds

PUBLICATION-DATE: March 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Morozowich, Walter	Kalamazoo	MI	US	

APPL-NO: 10/ 224742 [PALM]
DATE FILED: August 21, 2002

RELATED-US-APPL-DATA:
Application 10/224742 is a division-of US application 09/122926, filed July 27, 1998, PENDING
Application is a non-provisional-of-provisional application 60/054012, filed July 29, 1997,

INT-CL: [07] A61 K 38/13, A61 K 31/70, A61 K 31/58, A61 K 31/56, A61 K 31/496, A61 K 31/4745, A61 K 31/337, A61 K 31/355

US-CL-PUBLISHED: 424/400; 514/9, 514/176, 514/177, 514/283, 514/449, 514/365, 514/36, 514/458, 514/254.07, 514/389
US-CL-CURRENT: 424/400; 514/176, 514/177, 514/254.07, 514/283, 514/36, 514/365, 514/389, 514/449, 514/458, 514/9

ABSTRACT:

The present invention provides a novel pharmaceutical composition based on the use of a particular oil phase which comprises a lipophilic, pharmaceutically active agent, a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di-unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length, one or more pharmaceutically acceptable solvents, and one or more pharmaceutically acceptable surfactants. The composition is in a form of self-emulsifying formulation which provides high concentration and high oral bioavailability for lipophilic compounds.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of the following provisional application: U.S. Serial No. 60/054,078, filed Jul. 29, 1997, under 35 USC 119(e)(i).

DOCUMENT-IDENTIFIER: US 20030044434 A1
TITLE: Self-emulsifying formulation for lipophilic compounds

CLAIMS:

19. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable surfactant is Polyoxyl 40 hydrogenated castor oil, Polyoxyl 35 castor oil, Solutol HS-15, Tagat TO, Peglicol 6-oleate, Polyoxyethylene stearates, Poloxamers, Polysorbates, or Saturated Polyglycolyzed Glycerides.

US 20030044434A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0044434 A1**

Gao et al. (43) **Pub. Date: Mar. 6, 2003**

(54) **SELF-EMULSIFYING FORMULATION FOR LIPOPHILIC COMPOUNDS**

(76) Inventors: **Ping Gao**, Portage, MI (US); **Walter Morozowich**, Kalamazoo, MI (US)

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(21) Appl. No.: **10/224,742**

(22) Filed: **Aug. 21, 2002**

Related U.S. Application Data

(62) Division of application No. 09/122,926, filed on Jul. 27, 1998.

(60) Provisional application No. 60/054,012, filed on Jul. 29, 1997.

Publication Classification

(51) **Int. Cl.**[7] **A61K 38/13**; A61K 31/70; A61K 31/58; A61K 31/56; A61K 31/496; A61K 31/4745; A61K 31/337; A61K 31/355

(52) **U.S. Cl.** **424/400**; 514/9; 514/176; 514/177; 514/283; 514/449; 514/365; 514/36; 514/458; 514/254.07; 514/389

(57) **ABSTRACT**

The present invention provides a novel pharmaceutical composition based on the use of a particular oil phase which comprises a lipophilic, pharmaceutically active agent, a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di-unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length, one or more pharmaceutically acceptable solvents, and one or more pharmaceutically acceptable surfactants. The composition is in a form of self-emulsifying formulation which provides high concentration and high oral bioavailability for lipophilic compounds.

DOCUMENT-IDENTIFIER: US 6531139 B1
TITLE: Self-emulsifying formulation for lipophilic compounds

CLAIMS:

1. A pharmaceutical composition comprising; (a) a lipophilic, pharmaceutically active agent, (b) a mixture consisting essentially of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di-unsaturated tatty acid esters of glycerol having sixteen to twenty-two carbon chain length, (c) one or more pharmaceutically acceptable solvents, and (d) one or more pharmaceutically acceptable surfactants; wherein the solvent is propylene glycol, polypropylene glycol, polyethylene glycol, glycerol, ethanol, dimethyl isosorbide, glycofurol, propylene carbonate, dimethyl acetamide, or a mixture thereof; wherein said surfactant is Polyoxyl 40 hydrogenated castor oil, Polyoxyl 35 castor oil, polyethylene glycol 12-hydroxy stearate, polyoxyethylene glyceryl trioleate, Peglicol 6-oleate, Polyoxyethylene stearates, Poloxamers, Polysorbates, or Saturated Polyglycolyzed Glycerides; with the proviso that said lipophilic, pharmaceutically active agent has a LOG P value .gtoreq.2, an intrinsic aqueous solubility .ltoreq.0.1 in the pH range of 1 to 8 and a solubility greater than 1 mg/ml in the mixture of b, c and d as defined herein.

US006531139B1

(12) **United States Patent**
Gao et al.

(10) **Patent No.: US 6,531,139 B1**
(45) **Date of Patent: *Mar. 11, 2003**

(54) **SELF-EMULSIFYING FORMULATION FOR LIPOPHILIC COMPOUNDS**

(75) Inventors: **Ping Gao**, Portage; **Walter Morozowich**, Kalamazoo, both of MI (US)

(73) Assignee: **Pharmacia & Upjohn Company**, Kalamazoo, MI (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/122,926**

(22) Filed: **Jul. 27, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/054,078, filed on Jul. 29, 1997.

(51) **Int. Cl.**[7] **A61K 9/48**; A61K 31/44; A61K 31/35

(52) **U.S. Cl.** **424/400**; 424/451; 424/455; 424/456; 514/2; 514/9; 514/169; 514/315; 514/336; 514/456; 514/459; 514/460; 514/557; 514/558; 514/560; 514/573; 514/937; 514/11

(58) **Field of Search** 424/400, 451, 424/455, 456; 514/2, 9, 169, 459, 460, 557, 558, 560, 937–943, 315, 336, 456, 573

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GB	2 228 198 A		8/1990
GB	2 257 359 B		10/1996
WO	94/08603	*	4/1994
WO	WO95/30670		11/1995
WO	WO96/39142		12/1996
WO	WO98/22106		5/1998

* cited by examiner

Primary Examiner—Gollamudi S. Kishore
(74) *Attorney, Agent, or Firm*—Lucy X. Yang; Austin W. Zhang; Sidney B. Williams, Jr.

(57) **ABSTRACT**

The present invention provides a novel pharmaceutical composition based on the use of a particular oil phase which comprises a lipophilic, pharmaceutically active agent, a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length, one or more pharmaceutically acceptable solvents, and one or more pharmaceutically acceptable surfactants. The composition is in a form of self-emulsifying formulation which provides high concentration and high oral bioavailability for lipophilic compounds.

39 Claims, No Drawings

First Hit Fwd Refs

L8: Entry 99 of 160 File: USPT Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6121313 A
TITLE: Pharmaceutical composition in a form of self-emulsifying formulation for lipophilic compounds

CLAIMS:

19. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable surfactant is Polyoxyl 40 hydrogenated castor oil, Polyoxyl 35 castor oil, Solutol HS-15, Tagat TO, Peglicol 6-oleate, Polyoxyethylene stearates, Poloxamers, Polysorbates, or Saturated Polyglycolyzed Glycerides.

US006121313A

United States Patent [19]

Gao et al.

[11] Patent Number: 6,121,313

[45] Date of Patent: Sep. 19, 2000

[54] **PHARMACEUTICAL COMPOSITION IN A FORM OF SELF-EMULSIFYING FORMULATION FOR LIPOPHILIC COMPOUNDS**

[75] Inventors: **Ping Gao**, Portage; **Walter Morozowich**, Kalamazoo, both of Mich.

[73] Assignee: **Pharmacia & Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **09/123,069**

[22] Filed: **Jul. 27, 1998**

Related U.S. Application Data

[60] Provisional application No. 60/054,078, Jul. 29, 1997.

[51] **Int. Cl.**[7] **A61K 31/35**; A61K 31/19; A61K 31/20

[52] **U.S. Cl.** **514/459**; 514/460; 514/557; 514/558; 514/560

[58] **Field of Search** 514/459, 460, 514/557, 558, 560

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Russell Travers
Attorney, Agent, or Firm—Lucy X. Yang

[57] **ABSTRACT**

The present invention provides a novel pharmaceutical composition based on the use of a particular oil phase which comprises a pyranone compound as a pharmaceutically active agent, a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length, one or more pharmaceutically acceptable solvents, and one or more pharmaceutically acceptable surfactants. The composition is in a form of a self-emulsifying formulation which provides high concentration and high oral bioavailability for lipophilic pyranone compounds.

34 Claims, No Drawings

US-PAT-NO: 5681552
DOCUMENT-IDENTIFIER: US 5681552 A

TITLE: Clear cosmetic stick composition containing a combination of anionic and non-ionic surfactants

DATE-ISSUED: October 28, 1997

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/65; 424/78.02, 424/78.08, 424/78.18, 512/1, 514/944, 514/946

CLAIMS:

We claim:

1. A clear stick composition, comprising alcohol and water, and a soap gelling agent, the soap gelling agent being included in an amount so as to gel and to form the stick composition, the composition further including, as a clarifying agent, a combination of both (a) at least one anionic surface active agent and (b) at least one non-ionic surface active agent, the at least one non-ionic surface active agent including a straight chain primary alkoxylated alcohol, other than nonoxynol-10, ceteareth-12, ceteareth-20, ceteareth-30, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PPG-2 ceteareth-9, oleth-10-, oleth-5 and PEG-40 castor oil, the combination of anionic and non-ionic surface active agents being included in the composition in an amount so as to provide a clear stick composition, the at least one anionic surface active agent being included in the composition in an amount of 2-8% by weight, of the total weight of the composition, and the at least one non-ionic surface active agent being included in the composition in an amount of 2-8% by weight, of the total weight of the composition.

2. A clear stick composition according to claim 1, wherein the composition further includes a deodorant effective amount of a deodorant active material, whereby the composition is a clear deodorant stick composition.

3. A clear stick composition according to claim 2, wherein said deodorant active material is at least one selected from the group consisting of fragrances and antibacterial agents.

4. A clear stick composition according to claim 1, wherein the alcohol includes propylene glycol, and the soap gelling agent includes alkali metal salts of fatty acids.

5. A clear stick composition according to claim 4, wherein the composition includes, in percent by weight of the total weight of the composition, 55-80% propylene glycol, 9-25% water and 4-10% soap gelling agent.

6. A clear stick composition according to claim 1, wherein the composition includes, in percent by weight of the total weight of the composition, 4-6% of the at least one anionic surface active agent and 2-4% of the at least one

non-ionic surface active agent.

7. A clear stick composition according to claim 1, wherein said straight chain primary alkoxylated alcohol is a straight chain primary ethoxylated alcohol.

8. A clear stick composition according to claim 1, wherein said at least one non-ionic surface active agent has a hydrophile-lipophile balance of at least 24.

9. A clear stick composition according to claim 8, wherein the straight chain primary alkoxylated alcohol is a straight chain primary ethoxylated alcohol.

10. A clear stick composition according to claim 8, wherein the at least one anionic surface active agent includes sodium laureth-13 carboxylate.

11. A clear stick composition according to claim 10, wherein the at least one non-ionic surface active agent is selected from the group consisting of Ceteareth-55, C14-15 Pareth-2.25 and C14-15 Pareth-13.

12. A clear stick composition according to claim 11, wherein the at least one non-ionic surface active agent includes Ceteareth-55.

13. A clear stick composition according to claim 7, wherein the composition further includes a deodorant effective amount of a deodorant active material, whereby the composition is a clear deodorant stick composition.

14. A clear deodorant stick composition according to claim 13, wherein said deodorant active material is at least one selected from the group consisting of fragrances and antibacterial agents.

15. A clear stick composition according to claim 1, wherein the composition further includes a deodorant effective amount of a deodorant active material, whereby the composition is a clear deodorant stick composition.

16. A clear deodorant stick composition according to claim 15, wherein said deodorant active material is at least one selected from the group consisting of fragrances and antibacterial agents.

17. A clear stick composition according to claim 1, wherein the at least one anionic surface active agent is selected from the group consisting of long-chain fatty acids, sulfosuccinates, alkyl sulfates, phosphates and sulfonates.

18. A clear stick composition according to claim 1, wherein the at least one non-ionic surface active agent includes polyethylene oxide groups.

19. A clear stick composition according to claim 1, wherein the soap gelling agent includes salts of fatty acids, the fatty acids having a carbon chain length in a range of C.sub.12 -C.sub.22, at least some of the salts being salts of fatty acids having carbon chain length of at least one of C.sub.20 and C.sub.22.

20. A clear stick composition according to claim 1, wherein the at least one anionic surface active agent includes a sodium salt of methyl carboxy derivatives of ethoxylated lauryl alcohol.

21. A clear stick composition according to claim 1, wherein the soap gelling

agent includes sodium laurate, sodium myristate, sodium palmitate, sodium stearate, sodium arachidate and sodium behenate.

22. A packaged clear deodorant stick composition, comprising the clear deodorant stick composition of claim 15 in a dispensing package, wherein the dispensing package is made of a styrene-butadiene copolymer.

23. A packaged clear deodorant stick composition according to claim 22, wherein the dispensing package is clear.

24. A packaged clear stick composition, comprising the clear stick composition of claim 1 in a dispensing package, wherein the dispensing package is made of a styrene-butadiene copolymer.

25. A packaged clear deodorant stick composition according to claim 24, wherein the dispensing package is clear.

26. A method of reducing body malodor, comprising rubbing the clear deodorant stick composition of claim 15 on axillary regions of a human body.

27. A method of reducing body malodor, comprising rubbing the clear deodorant stick composition of claim 13 on axillary regions of human body.

28. A method of reducing body malodor, comprising rubbing the clear deodorant stick composition of claim 2 on axillary regions of a human body.

29. A clear stick composition, comprising alcohol and water, and a soap gelling agent, the soap gelling agent being included in an amount so as to gel and to form the stick composition, the composition further including, as a clarifying agent, a combination of both (a) at least one anionic surface active agent and (b) at least one non-ionic surface active agent, the at least one non-ionic surface active agent including an alkoxylate homopolymer, other than nonoxynol-10, ceteareth-12, ceteareth-20, ceteareth-30, PEG-5 cocamide, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, oleth-5, oleth-10, PEG-40 castor oil, polysorbate 20, polysorbate 60, polysorbate 80 and PEG-8 stearate, the combination of anionic and non-ionic surface active agents being included in the composition in an amount so as to provide a clear stick composition, the at least one anionic surface active agent being included in the composition in an amount of 2-8% by weight, of the total weight of the composition, and the at least one non-ionic surface active agent being included in the composition in an amount of 2-8% by weight, of the total weight of the composition.

30. A clear stick composition according to claim 29, wherein the composition includes, in percent by weight of the total weight of the composition, 4-6% of the at least one anionic surface active agent and 2-4% of the at least one non-ionic surface active agent.

31. A clear stick composition according to claim 29, wherein said alkoxylate homopolymer is an ethoxylate homopolymer.

32. A clear stick composition according to claim 29, wherein said at least one non-ionic surface active agent has a hydrophile-lipophile balance of at least 24.

33. A clear stick composition, comprising alcohol and water, and a soap gelling agent, the soap gelling agent being included in an amount so as to gel

and to form the stick composition, the composition further including, as a clarifying agent, a combination of both (a) at least one anionic surface active agent and (b) at least one non-ionic surface active agent, the at least one non-ionic surface active agent having a hydrophile-lipophile balance of at least 24, the combination of anionic and non-ionic surface active agents being included in the composition in an amount so as to provide a clear stick composition.

34. A clear stick composition according to claim 33, wherein the at least one anionic surface active agent and the at least one non-ionic surface active agent are each included in the composition in an amount of 2-8% by weight, of the total weight of the composition.

35. A clear stick composition according to claim 34, wherein the composition includes, in percent by weight of the total weight of the composition, 4-6% of the at least one anionic surface active agent and 2-4% of the at least one non-ionic surface active agent.

US005681552A

United States Patent [19]

Shevade et al.

[11] Patent Number: 5,681,552

[45] Date of Patent: Oct. 28, 1997

[54] **CLEAR COSMETIC STICK COMPOSITION CONTAINING A COMBINATION OF ANIONIC AND NON-IONIC SURFACTANTS**

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[73] Assignee: **The Mennen Company**, Morristown, N.J.

[21] Appl. No.: **448,104**

[22] Filed: **May 23, 1995**

[51] **Int. Cl.**[6] **A61K 7/32**

[52] **U.S. Cl.** **424/65**; 424/78.02; 424/78.08; 424/78.18; 512/1; 514/944; 514/946

[58] **Field of Search** 424/65, 78.02, 424/78.08, 78.18; 512/1; 514/944, 946

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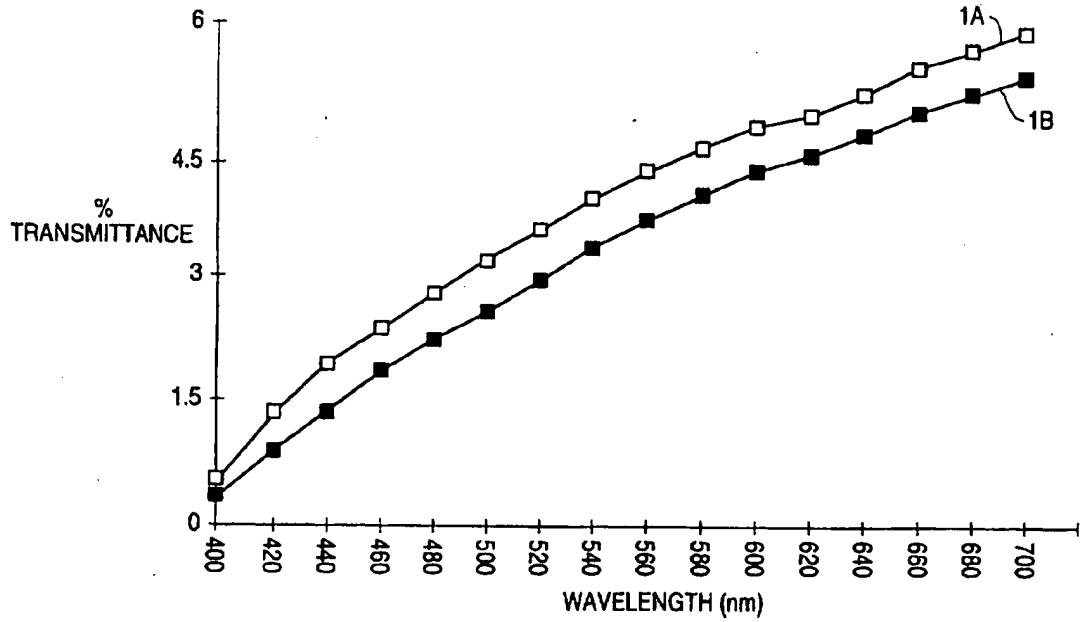
Attorney, Agent, or Firm—Antonelli, Terry, Stout & Kraus, LLP

[57] **ABSTRACT**

Disclosed are clear, soap-gelled cosmetic (e.g., deodorant) stick compositions, containing alcohol and water, and including a combination of anionic (e.g., sodium laureth-13 carboxylate) and non-ionic (e.g., Ceteareth-55) surfactants as a clarifying agent. The non-ionic surfactants preferably include ethoxylated alcohols, and preferably have an HLB≧24. The compositions can include various cosmetically active materials, including deodorant active materials (fragrance, Triclosan, etc.). The compositions have superior clarity and maintain superior clarity over extended periods of time, have improved (smoother) glide over the skin and a smoother surface, exhibit reduced syneresis in K-resin and polypropylene dispensing packages, and are easy to manufacture and have high gelling temperatures.

35 Claims, 5 Drawing Sheets



US-PAT-NO: 5189066
DOCUMENT-IDENTIFIER: US 5189066 A

TITLE: Pharmaceutical compositions of tebufelone

DATE-ISSUED: February 23, 1993

INVENTOR-INFORMATION:

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Bruns; Alan E.	Okeana	OH		

US-CL-CURRENT: 514/678; 514/689, 514/941, 514/960, 514/961

CLAIMS:

What is claimed is:

1. A composition consisting essentially of 1-3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl-5-hexyn-1-one as a drug active at a concentration of at least about 15% of the composition, and the balance a pharmaceutically-acceptable vehicle, the composition having the following properties:

(1) being a homogeneous liquid at 37.degree. C.,

(2) providing solubilization of the drug active at a level of at least 1 mg/mL in 0.1N HCl at 20.degree. C., and

(3) providing solubilization of 20 mg of the drug active in 500 mL of simulated intestinal fluid in 5 minutes;

the vehicle comprising a surfactant or mixture of surfactants, the vehicle having the following properties:

(a) being a homogeneous liquid at 37.degree. C.,

(b) having an HLB of from about 9 to about 13,

(c) forming a stable dispersion in water at 20.degree. C. at concentrations of 10%;

whereby the absorption of the drug active from the gastrointestinal tract is substantially greater for the composition when perorally administered than for conventional solid dosage forms of the drug active.

2. The composition of claim 1 wherein the vehicle additionally has the following properties:

(d) being soluble in isopropanol at 20.degree. C. at concentrations of 10%, and

(e) being soluble in cottonseed oil at 20.degree. C. at concentrations of 1%.

3. The composition of claim 1 wherein the surfactant is selected from the group consisting of polysorbate 81, poloxamer 182, poloxamer 183, poloxamer 184, PEG-25 glyceryl trioleate, and polyoxyl 35 castor oil, and mixtures thereof.

4. The composition of any of claims 1, 2 or 3 wherein the vehicle consists essentially of the surfactant or surfactant mixture.

5. The composition of claim 1 wherein the vehicle also comprises a lipophilic solvent selected from the group consisting of a triglyceride or a mixture of triglycerides having fatty chains of from about 6 to about 10 carbon atoms, straight-chain saturated fatty acids having from about 6 to about 10 carbon atoms, and straight-chain unsaturated fatty acids having from about 12 to about 18 carbon atoms, and mixtures thereof.

6. The compositions of claim 5 wherein the surfactant is selected from the group consisting of polysorbate 80, polysorbate 81, poloxamer 182, poloxamer 183, poloxamer 184, PEG-25 glyceryl trioleate and polyoxyl 35 castor oil, and mixtures thereof.

7. The composition of claim 6 wherein the vehicle consists essentially of from about 25% to about 85% of a lipophilic solvent which is selected from the group consisting of caprylic/capric triglyceride, oleic acid and linoleic acid; and from about 15% to about 75% of the surfactant.

8. The composition of claim 3 consisting essentially of from about 15% to about 20% tebufelone, from about 35% to about 45% polyoxyl 35 castor oil, and from about 35% to about 45% poloxamer 182.

9. The composition of claim 5 consisting essentially of from about 15% to about 20% tebufelone, from about 4% to about 6% polyoxyl 35 castor oil, from about 20% to about 25% poloxamer 182, and from about 50% to about 60% caprylic/capric triglyceride.

10. A composition consisting essentially of 1-3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl-5-hexyn-1-one as a drug active at a concentration of at least about 15% of the composition, and the balance a pharmaceutically-acceptable vehicle, the composition having the following properties:

(1) being a homogeneous liquid at 37.degree. C.,

(2) providing solubilization of the drug active of at least 1 mg/mL in 0.1N HCl at 20.degree. C., and

(3) providing solubilization of 20 mg of the drug active in 500 mL of simulated intestinal fluid in 5 minutes;

the vehicle comprising triglycerides interesterified with polyethylene glycol, such that its HLB is from about 3 to about 7; whereby the absorption of the drug active from the gastrointestinal tract is substantially greater for the composition when perorally administered than for conventional solid dosage forms of the drug active.

11. The composition of claim 10 wherein the triglycerides interesterified with polyethylene glycol are glycolysed ethoxylated glycerides obtained by partial hydrolysis of natural vegetable oils.

12. The composition of claim 11 wherein the triglycerides interesterified with polyethylene glycol are glycolysed ethoxylated glycerides obtained by partial hydrolysis of corn oil with polyethylene glycol 400.

13. The composition of any of claims 10, 11 or 12 wherein the vehicle consists essentially of the triglycerides interesterified with polyethylene glycol.

14. A pharmaceutical unit dosage form comprising a composition of any of claims 3, 6, 8, 9 or 12 in a soft gelatin capsule shell.

15. A pharmaceutical unit dosage form comprising a composition of any of claims 3, 6, 8, 9 or 12 in a sealed hard gelatin capsule shell.

16. The composition of claim 1 wherein the surfactant is 100% polysorbate 81.

17. The composition of claim 1 wherein the surfactant is 100% PEG-25 glyceryl trioleate.

18. The composition of claim 1 wherein the surfactant is 100% poloxamer 183.

19. The composition of claim 1 wherein the surfactant is 100% poloxamer 184.

20. The composition of claim 1 wherein the surfactant is from about 25% to about 75% poloxyl 35 castor oil and from about 25% to about 75% poloxamer 182.

21. The composition of claim 1 wherein the surfactant is from about 10% to about 25% polysorbate 80 and from about 75% to about 90% poloxamer 182.

22. A method for obtaining good absorption of the drug active from the gastrointestinal tract by perorally administering the composition of any of claims 1, 3, 6, 10 or 11.

US005189066A

United States Patent [19]

Kelm et al.

[11] Patent Number: 5,189,066

[45] Date of Patent: Feb. 23, 1993

[54] **PHARMACEUTICAL COMPOSITIONS OF TEBUFELONE**

[75] Inventors: **Gary R. Kelm**, Cincinnati; **Alan E. Bruns**, Okeana, both of Ohio

[73] Assignee: **The Procter & Gamble Company**, Cincinnati, Ohio

[21] Appl. No.: **732,951**

[22] Filed: **Jul. 19, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 440,178, Nov. 22, 1989, abandoned.

[51] **Int. Cl.**[5] **A61K 31/12**

[52] **U.S. Cl.** **514/678**; 514/689; 514/960; 514/961; 514/941

[58] **Field of Search** 514/678, 689, 960, 961, 514/941

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Attorney, Agent, or Firm—M. B. Graff, IV; J. D. Schaeffer; T. H. O'Flaherty

[57] **ABSTRACT**

The subject invention involves compositions, consisting essentially of the drug active 1-3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl-5-hexyn-1-one (tebufelone) at a concentration of at least about 15%, and the balance a pharmaceutically-acceptable vehicle. The vehicle is formulated such that the compositions are homogeneous liquids at 37° C. and provide good solubilization of the drug active.

22 Claims, No Drawings